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THE DEVELOPMENT OF THE CRANIAL ARTERIES IN THE HUMAN EMBRYO

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With five plates (two colored) and thirteen text figures

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THE DEVELOPMENT OF THE CRANIAL ARTERIES IN THE HUMAN EMBRYO[1]

INTRODUCTION

The literature is singularly incomplete respecting the development of the cerebral arteries. This became apparent in connection with a study of the circle of Willis and its anomalies prepared by the writer for a monograph on intracranial arterial aneurysms by Dandy (1944). The initial interest in the embryonic derivation of the arteries concerned led to an analysis of all the cranial arteries, which is the scope of this paper. Since Evans' account of the head arteries in the Keibel and Mall *Manual* (1912), based on his own investigations and those of Tandler (1902), Mall (1905), and others, there have appeared two well known papers. Streeter (1918) described the underlying principles in the formation of the cranial vascular system and the adjustment of the blood vessels to growth changes in the brain and environment. He was chiefly concerned, however, with the development of the drainage channels, in particular the dural sinuses. Congdon (1922) fully described the evolution of the aortic arch system, including significant features in the origin of three cerebral arteries, the carotid, the basilar, and the vertebral. To supplement these fundamental studies, seven stages in the embryonic configuration of all the arteries in the region of the head are presented. During the preparation of this outline, three individual arteries, two of them temporary and one permanent, required particularly intensive study. The ophthalmic artery in recognizable adult form emerges relatively late in the embryo and only after a series of modifications which involve the temporary stapedial artery. The formation of the human stapedial artery and certain details concerning its retrogression have not been previously published. Another temporary artery, here named the "primitive trigeminal," was observed to be often conspicuous and always significant in relation to the development of several permanent arteries and is described for the first time as found in the human embryo. A recapitulation of the essential features of these individual arteries, discussed fully in the last three sections of this paper, will be found in the opening outline of stages, which covers all the cranial arteries.

The present study is based on the graphic, profile reconstructions of 22 sectioned embryos of the Carnegie Collection. These range from 3½ to 7 weeks (estimated ovulation age) and from 3 mm. (20 somites) in crown-rump length, when the primitive internal carotid artery appears, to approximately 40 mm., when the definitive adult origin of essentially all the cranial arteries is established. Using the enlarged photographic prints of serial sections of the embryos (or, in a few cases, tracings obtained on the Edinger apparatus), the reconstructions were built up by successive tracings on transparent paper or were plotted on millimeter paper. Employing both methods, many embryos were reconstructed in two or three planes (table 1). Thus, the standard lateral, horizontal, and coronal views gave a working basis with the advantages of the three-dimensional model, and, in addition, permitted much detail and accuracy in reference to the smaller arteries and their environmental relations. Certain details were clarified by microscopic study of other embryos not available for reconstruction; in two of these cases, as noted in the text, a partial freehand reconstruction on millimeter paper was feasible. The work was occasionally facilitated by existing models of the brain, aortic arches, or cerebral vessels of several embryos of the series, but none of these were used in preparing the present illustrations, which were made by the writer.

I wish to thank all those to whom I am indebted in connection with the preparation of this paper, which would have been impossible without the many courtesies, critical judgment, or assistance of Dr. George W. Corner, Dr. George L. Streeter, and Mr. James F. Didusch, of the Carnegie Institution of Washington. Particular thanks are also extended to Dr. David Bodian, Dr. William L. Straus, Jr., and Dr. Joseph Earle Moore, for review of the manuscript and many helpful suggestions. It is a great pleasure to express my gratitude to the late Dr. Walter E. Dandy, with whom I was long associated as a medical illustrator,

[1] The author was formerly on the Neurological Service of Dr. Walter E. Dandy, Johns Hopkins Hospital and Medical School. The embryological material was provided by the Department of Embryology of the Carnegie Institution of Washington.

and who inspired the study and generously made the grant necessary for its completion. Finally, I wish to pay tribute to the memory of the late Professor Max Brödel, whose personal influence I had the privilege of enjoying much longer than was the good fortune of most of his students.

STAGES IN THE DEVELOPMENT OF THE CRANIAL ARTERIES

The order of appearance of all the definitive cranial arteries cannot be stated categorically because of the well known existence of individual variation, particularly in the younger embryos. It was found, however, that the sequence of events fell logically into eight stages including the adult configuration, and more than one embryo, including several from the literature, was considered in reference to each. Table 1

TABLE 1

EMBRYOS GRAPHICALLY RECONSTRUCTED. CORRELATION OF SIZE AND AGE GROUP WITH THE DEVELOPMENT OF THE AORTIC ARCH SYSTEM AND THE CRANIAL ARTERIES

EMBRYO NO.	LENGTH (MM.)	VIEWS RECONSTRUCTED	FIGURE	CHARACTERISTIC FEATURES OF:	
				Individual embryo	Stage in general
TIME OF ESTABLISHMENT OF 1ST ARCH; 2D ARCH BEGINNING; ESTIMATED OVULATION AGE* 24 ± 1 DAYS					
2053.. (xi†)	3 (20 som.)	Bilat. Coron.	37, pl. 4 43, pl. 5	Primitive internal carotid and trigeminal arteries are branches of first arch; latter artery supplies cranial end of primordial hindbrain channel.	Establishment of primordial vascular system. Primordial hindbrain channel serves temporarily as vein for head; it is supplied by presegmental branches of paired ("dorsal") aorta.
TIME OF ESTABLISHMENT OF 2D AND 3D ARCHES; BEGINNING INVOLUTION OF 1ST ARCH; ESTIMATED OVULATION AGE 28 ± 1 DAYS					
836.. (xiii)	4	Bilat. Horiz.	38, pl. 4 39, pl. 4	Longitudinal neural arteries in formation, supplied by trigeminal and otic arteries (presegmental branches of paired "dorsal" aorta).	First stage in differentiation of supply and drainage channels. Disappearance of primordial hindbrain channel; resulting emergence of bilateral longitudinal neural arteries, which precede the basilar.
TIME OF ESTABLISHMENT OF 4TH ARCH; PULMONARY ARCH IN FORMATION; INVOLUTION OF 1ST AND 2D ARCHES; ESTIMATED OVULATION AGE 29 ± 1 DAYS					
588.. (xiii)	4	Bilat. Horiz. Coron.	1*a* 1*b* 44, pl. 5	Early form of mandibular and hyoid arteries; dorsal and ventral ends more or less continuous.	Bilateral longitudinal neural artery supplied by trigeminal artery cranially, reinforced by first cervical segmental artery caudally. Establishment of cranial and caudal divisions of internal carotid artery. (STAGE 1: fig. 14, pl. 1; fig. 22, pl. 2.)
1380.. (xiv)	5.7	Bilat. Coron.	....	Later form of mandibular and hyoid arteries; dorsal remnants only. Ventral pharyngeal artery.	
2841.. (xiv)	5.3	L. lat. Horiz.	2*a* 2*b*; 30, pl. 3	Dorsal remnants of mandibular (small) and hyoid (large) arteries. Ventral pharyngeal artery.	Basilar artery in formation from bilateral neural arteries, which are supplied cranially by new posterior communicating arteries (caudal divisions of carotids), sometimes reinforced by dwindling trigeminal and hypoglossal arteries. (STAGE 2: fig. 15, pl. 1; fig. 23, pl. 2.)
3960.. (xiv)	5.5	R. lat. Horiz.	3*a* 3*b*, *c*	Large ventral pharyngeal artery supplies major substance of first two pharyngeal bars. Primitive dorsal ophthalmic artery to lens primordium.	

* Estimates based on Heuser and Streeter's (1941) curve of length and age in the macaque.

† Roman numerals indicate developmental horizons of the Carnegie Collection, Streeter (1942, 1945, 1948). Groups xix through xxi are provisional.

(*Continued on following page*)

TABLE 1—*Continued*

Embryo no.	Length (mm.)	Views reconstructed	Figure	Characteristic features of:	
				Individual embryo	Stage in general
Time of establishment of pulmonary arch; splitting of aortic sac; estimated ovulation age 32 ± 1 days					
4782.. (xv)	9	Horiz.	.....	Intermediate stage in formation of basilar artery. Caroticobasilar (trigeminal) anastomosis large on one side.	Vertebral artery in formation. Beginning differentiation of cerebral arteries. Cranial division of internal carotid constitutes a primitive olfactory artery. Optic supply still plexiform but includes two primitive ophthalmic branches of carotid, one dorsal and one ventral. Stem of hyoid artery now at cranial edge of hyoid bar. Ventral pharyngeal artery accompanies mandibular end of chorda tympani nerve to mandibular root of fifth nerve. (Stage 3: fig. 16, pl. 1; fig. 24, pl. 2.)
617.. (xvi)	7	R. lat. Horiz.	..... 4*b*; 31, pl. 3	Late stage in formation of basilar; irregular with many islands.	
1121.. (xvi)	11.8	Bilat. Horiz. Coron.	.... 45, pl. 5	Island at caudal end of basilar. Interrupted remnants of caroticobasilar anastomosis. Early stage in formation of vertebral artery.	
163.. (xvi)	9	L. lat. Horiz.	4*a*	Basilar completed. Basilar remnant of caroticobasilar anastomosis. Anastomosis of cervical segmentals to form vertebral artery nearly complete.	
Time of interruption of right pulmonary arch and of "branchial period"; estimated ovulation age 35 ± 1 days					
1771.. (xvii)	12.5	Bilat. Horiz.	5*a* 5*b*	Late stage in formation of vertebral artery. Differentiation of cerebral arteries well advanced.	Vertebral artery complete but irregular; origin still low on paired aorta. A secondary branch of the hyoid artery constitutes the new stapedial artery, which has anastomosed with distal (mandibular) end of ventral pharyngeal artery at mandibular nerve root. Early stage in formation of anterior cerebral as a secondary branch of primitive olfactory artery. Derivative of primitive dorsal ophthalmic artery enters fetal ocular cleft as definitive hyaloid artery. Components of external carotid artery. (Stage 4: fig. 17, pl. 1; fig. 25, pl. 2.)
544.. (xvii)	11.5	Bilat. Horiz.	40, pl. 4 41, pl. 4	All cerebral arteries relatively primitive and plexiform. Bilateral retention of caroticobasilar (trigeminal) anastomosis in prominent form in both embryos.	
940.. (xvii)	14	Bilat. Horiz. Coron.	6 32, pl. 3; 42, pl. 4 46, pl. 5		
6520.. (xvii)	12.9	Horiz.	.....	Differentiation of cerebral arteries advanced except at caudal part of hindbrain.	
End of period of rapid descent of heart and arteries; aortic arch sharply bent; estimated ovulation age 40 ± 1 days					
144.. (xviii)	16	L. lat.	.....	These embryos are similar and resemble the 15.5-mm. and 17.8-mm. embryos of Evans (1912) and Thyng (1914), respectively.	Vertebral artery regular with origin moved to level of ductus arteriosus. Stapedial artery has three (mandibular, maxillary, and ophthalmic) branches. New permanent stem of ophthalmic artery, including primary optic branches. Middle and anterior cerebrals advanced. Primitive olfactory artery dwindling. Plexus in region of anterior communicating artery. Most cerebral arteries recognizable. Four or five branches of external carotid. (Stage 5: fig. 18, pl. 1; fig. 26, pl. 2.)
1390.. (xix)	18	Bilat. Horiz.	7*a* 7*b*; 33, pl. 3		

(*Continued on following page*)

TABLE 1—*Continued*

Embryo no.	Length (mm.)	Views reconstructed	Figure	Characteristic features of: Individual embryo	Stage in general
Summit of definitive aortic arch at superior thoracic aperture; estimated ovulation age 44 ± 1 days					
6202.. (xx)	21	Bilat. Horiz.	..... 34, pl. 3	Anterior communicating artery plexiform.	Circle of Willis completed by anterior communicating artery. Anterior cerebrals extend up between cerebral hemispheres; medial striate branches are remnants of primitive olfactory artery. Formation of orbital branches of ophthalmic artery by anastomosis between ophthalmic stem and supraorbital stapedial division. Stem of middle meningeal artery formed by anastomosis between maxillomandibular division of stapedial and internal maxillary artery. Most external carotid branches definitive. (Stage 6: fig. 19, pl. 1; fig. 27, pl. 2.)
460.. (xx)	21	Horiz.	.....	Anterior communicating artery present as single large channel. Island in basilar at fifth nerve level.	
966.. (xx)	23	L. lat. Coron.	..... 9; 47, pl. 5	Anterior communicating artery a single channel. Plexiform remnants of trigeminal anastomosis.	
632.. (xxi)	24	Bilat. Horiz.	8*a* 8*b;* 35, pl. 3	Anterior communicating artery large but duplicated. Interruption of stem of stapedial artery.	
Origin of right and left pulmonary branches in contact through most of their length; estimated ovulation age 52 ± 1 days					
6203..	39	L. lat. Horiz.	10*a* 10*b;* 36, pl. 3	Configuration of ophthalmic artery adult on left side, but primitive on right. Definitive medial striate arteries (remnants of primitive olfactory artery).	Circle of Willis recognizable in ventral (base) view of brain. Ophthalmic artery complete including lacrimal branch (segment of supraorbital division of stapedial). All stapedial branches annexed by ophthalmic and external carotid arteries. Stem of origin of all cerebral arteries is adult, although destination of several, notably the posterior cerebral and both inferior cerebellar arteries, conforms to the immature cerebral and cerebellar hemispheres. (Stage 7: fig. 20, pl. 1; fig 28, pl. 2.)
886..	43	L. lat. Horiz. Coron.	10*a* 10*b* 48, pl. 5	Small basilar remnant of trigeminal anastomosis. Striate branches of anterior cerebral in formation from remnants of primitive olfactory artery.	

shows the reconstructed embryos arranged in order of general development, and correlates successive stages of the cranial arteries and the aortic arch system. This table, patterned after that of Congdon (1922), includes 14 of the same embryos utilized by that author. Classification of the remaining 8 was determined from the development of the brain, arteries, and external form. The embryos listed in table 1, and noted in the text, are also classified in the age groups (age group xi, xii, etc.) currently being determined by Dr. Streeter (1942, 1945, this volume, and personal communication). These groups, of which 23 in all are contemplated, will carry through the first 7 weeks and will include embryos up to approximately 40 mm., "beyond [which] time the weekly increment in growth and weight is large enough to provide an adequate index of relative development."

Stage 1, Embryos Approximately 4–5 mm., Age Groups XIII, XIV

An embryo of 4 mm. (no. 588, fig. 1), which Streeter described as illustrative of the primary type of cranial circulation, constitutes a logical stage with which to begin the present outline. The arterial system is somewhat more advanced than in no. 836, which is also in age group xiii and will be described below (pl. 4, figs. 38, 39); and is less advanced than in no. 1380, of 5.7 mm., in age group xiv. In no. 1380 the optic vesicle is at a later stage, but, although no vessels could be traced in the substance of its first two

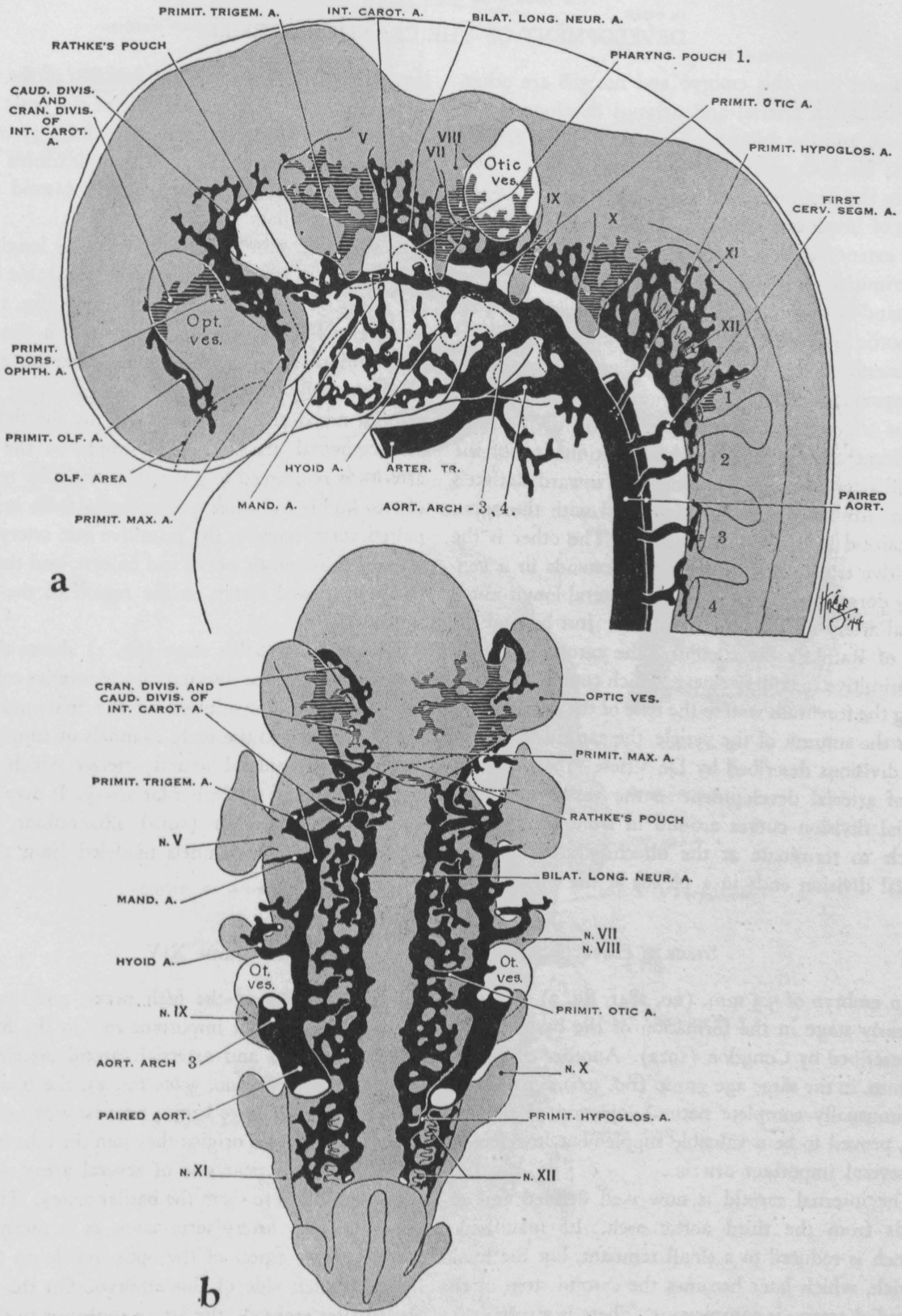

FIG. 1. Stage 1. Graphic reconstruction of the cranial arteries in a 4-mm. embryo (no. 588). Following the involution of the first two aortic arches, now represented by mandibular and hyoid arteries, the terminal end of the paired aorta of earlier stages (figs. 37, 38, pl. 4) is recognizable as the internal carotid artery originating from the third arch (*a*). The forebrain and optic vesicle are supplied by the primitive maxillary branch and the primary cranial division of the carotid; the caudal division courses over the midbrain. The emerging bilateral neural artery on the hindbrain wall (*b*) is also supplied by the carotid through the primitive trigeminal branch, supplemented by other presegmental branches of the original paired aorta in the otic and hypoglossal regions. The caudal end of the neural artery is fed by the first cervical segmental artery. ×50.

pharyngeal bars, this embryo and no. 588 are otherwise similar in arterial and nervous development of the head, and the following description holds true in general for both embryos.

Since the first and second aortic arches are in early stages of involution, the portion of paired ("dorsal") aorta extending from the third arch now represents the primitive internal carotid artery. In addition to the mandibular and hyoid arteries (replacing the first two aortic arches), there are other conspicuous mesial and lateral offshoots, and all together the carotid has the appearance of having just emerged from a plexus. At the trigeminal ganglion, the carotid divides into two branches. One, the cerebral continuation of the carotid artery, extends craniomesially toward Rathke's pouch, around which it is connected with the opposite carotid by plexiform channels. The other is the primitive trigeminal artery, which extends in a generally dorsal direction to join the bilateral longitudinal neural artery on the hindbrain wall. Just beyond the base of Rathke's diverticulum, the carotid gives off the primitive maxillary artery, which courses ventrally along the forebrain wall to the base of the optic vesicle. Near the summit of the vesicle, the carotid forms the two divisions described by De Vriese (1905) as typical of arterial development in the vertebrates. The cranial division curves around in front of the optic vesicle to terminate at the olfactory area, and the caudal division ends in a plexus at the mesencephalon. A small offshoot near the junction of the carotid division passes to the mesial face of the optic vesicle and represents a primitive ophthalmic artery, but supply to the future eye is highly plexiform at this stage and is contributed by both the carotid and its primitive maxillary branch.

In the hindbrain region, the bilateral longitudinal neural arteries have just become recognizable bordering a ventral mid-line nonvascular strip (fig. 1*b*) and are everywhere connected laterally with the primitive hindbrain plexus. The neural arteries are supplied cranially by the trigeminal divisions of the carotid, noted above, and caudally by the first cervical segmental arteries. This supply to the neural arteries is reinforced to a variable extent by remnants of two highly transitory presegmental branches of the paired aorta, namely, the primitive otic artery, at the level of the acoustic nerve and otocyst, and the primitive hypoglossal artery, in the region of the twelfth nerve.

To summarize, this stage (fig. 1) shows the early configuration of the internal carotid arteries coincident with the initial involution of the first and second aortic arches, and the early channels of supply to the bilateral longitudinal neural arteries which precede the development of the basilar artery. It may be compared with Streeter's (1918) illustrations (his pl. 2) of the venous channels modeled from the same embryo.

Stage 2, Embryos Approximately 5–6 mm., Age Group XIV

An embryo of 5.3 mm. (no. 2841, fig. 2) illustrates an early stage in the formation of the basilar artery as described by Congdon (1922). Another embryo of 5.5 mm. in the same age group (no. 3960, fig. 3), with an unusually complete natural injection of the vessels, proved to be a valuable supplement in reference to several important arteries.

The internal carotid is now well defined and extends from the third aortic arch. Its mandibular branch is reduced to a small remnant, but the hyoid branch, which later becomes the carotid stem of the stapedial artery, is conspicuous. There is a prominent vessel in the general position of the ventral part of the first two aortic arches. This is the "ventral pharyngeal artery" (Congdon, 1922), which extends craniolaterally from the aortic sac at the mid-line to the mandibular root of the fifth nerve, and, as will be shown later, has an important role in the formation of the stapedial and external carotid arteries.

In one embryo (no. 3960, fig. 3), the bilateral trigeminal arteries have begun retrogression, and dwindle at their carotid origin; they join the bilateral longitudinal neurals near one of several areas where the latter are fused to form the basilar artery. The primitive maxillary artery terminates, as formerly, on the caudoventral aspect of the optic vesicle on the more primitive left side of this embryo. On the right, as in all later embryos, the artery conforms to the lateral margins of Rathke's pouch, proceeding ventromesially to a terminal plexus on the mesial tip of the prosencephalon. The caudal division of the internal carotid has now formed a secondary anastomosis with the

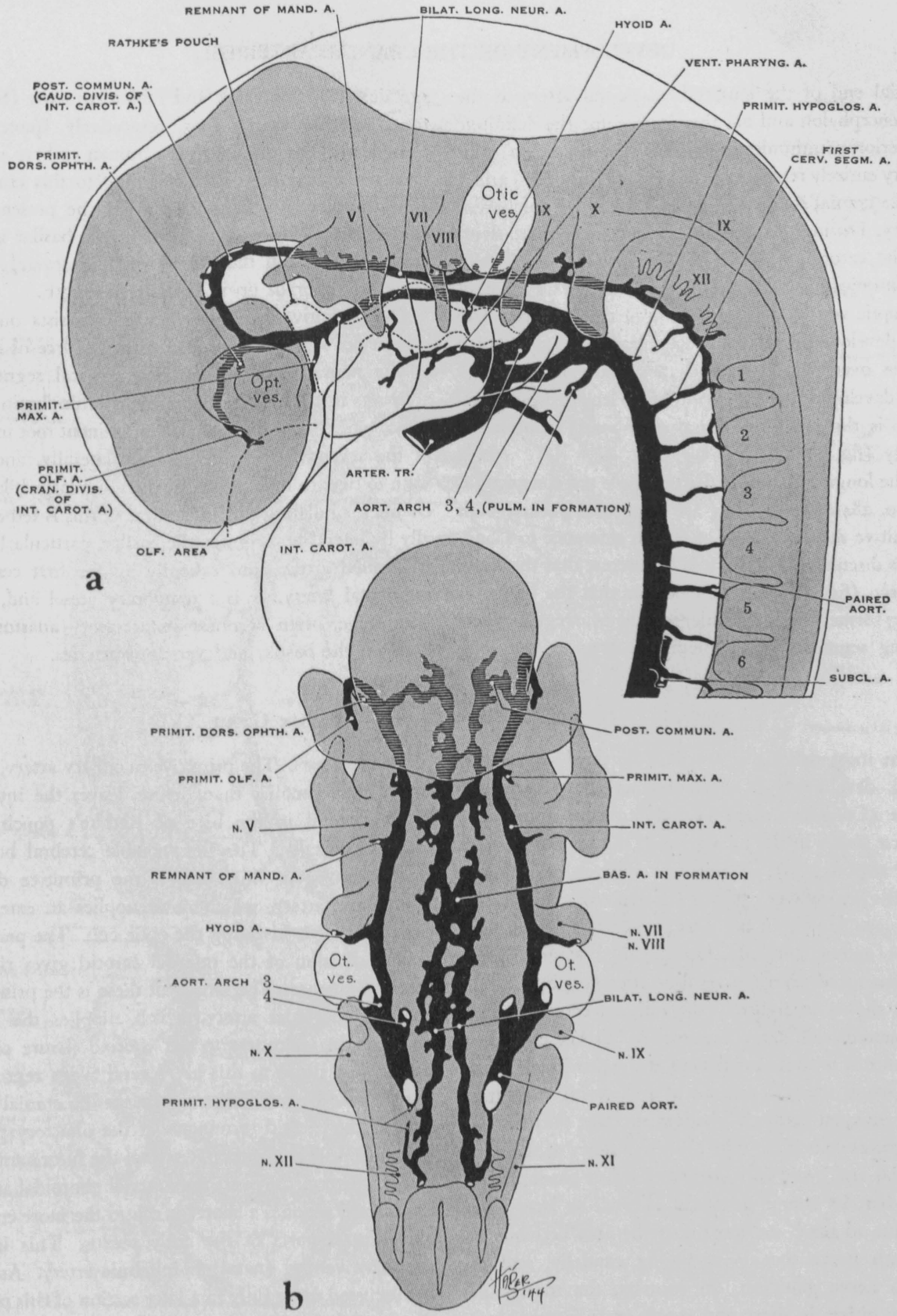

FIG. 2. Stage 2 (see also fig. 3). The cranial arteries in a 5.3-mm. embryo (no. 2841). The caudal division of the internal carotid has joined the bilateral longitudinal neural to form the definitive posterior communicating artery. The primitive trigeminal artery, no longer essential for supply to the cranial end of the neural artery, has disappeared. The basilar artery is being formed by consolidation of the neural arteries (*b*). A ventral pharyngeal artery supplies the greater part of the first two pharyngeal bars. ×37.5.

cranial end of the longitudinal neural artery at the mesencephalon and has thereby become the definitive posterior communicating artery. Soon (fig. 2) this artery entirely replaces the temporary trigeminal artery as the cranial source of blood to the neural or basilar artery. During the preceding stage, one or more twigs of the carotid, near its junction with the posterior communicating artery, passed to the mesial face of the optic vesicle. In the position of these vessels there has developed a relatively long lateral branch which passes over the dorsal and more caudal margin of the developing optic cup to the lens primordium. This is the primitive dorsal (temporal) ophthalmic artery (fig. 3).

The longitudinal neural arteries are not conspicuous in no. 2841 (fig. 2), but are large and packed with primitive red cells in no. 3960. In reference to Congdon's discussion (1922), it is of interest that the latter embryo (fig. 3) gives no evidence that the basilar is being formed from the enlargement of irregular alternating segments of the neural arteries as was long ago described for chick and rabbit embryos (Sterzi, 1904, and De Vriese, 1905, respectively, quoted by Congdon). The process in the human embryo is primarily a matter of fusion according to this embryo. This impression is substantiated by the presence of one or more islands in all parts of the basilar artery (most frequent in the caudal end) in several more advanced embryos up to 21 mm. in length.

The primitive hypoglossal artery persists on one side in no. 2841, but the chief caudal source of blood to the neural artery is the first cervical segmental artery as in the earlier stage. On the hindbrain wall in no. 3960 (fig. 3), between the prominent root masses of the seventh to eleventh nerves laterally, and the sixth to twelfth more mesially, there is a large bilateral channel paralleling the neural artery; this is fed cranially by lateral branches of the basilar, particularly the trigeminal artery, and caudally by the first cervical segmental artery. It is a temporary vessel and, in a later stage, often becomes an accessory anastomosis between the basilar and vertebral arteries.

Stage 3, Embryos Approximately 7–12 mm., Age Group XVI

The most striking advance of the third stage of arterial development, which brings the "branchial" phase (Congdon, 1922) to a close, is the appearance of first stages in the formation of the vertebral artery (no. 163, fig. 4*a*). The three embryos of different lengths which were fully reconstructed to cover this stage are similar in body form, nervous system, and aortic arches, but illustrate detailed stages in development of several cranial arteries (table 1).

As shown in figure 4, the internal carotid is now characteristically large and swollen in its cerebral part, in contrast with its small stem at the third aortic arch. The hyoid artery is prominent and, owing to shifting and unequal growth changes in the surrounding structures coincident with the ascendancy of the mandibular and hyoid bars over the third or glossopharyngeal bar, its course is caudal, as well as lateral and ventral, to reach its domain in the area between the seventh nerve root, now swung caudally, and the ninth nerve ganglion. In contrast, the mandibular artery either is short and small or is impossible to identify. The ventral pharyngeal artery, whose distal part accompanies the mandibular end of the chorda tympani nerve, supplies the bulk of the first two pharyngeal bars. The primitive maxillary artery, relatively much smaller than before, leaves the internal carotid lateral to the base of Rathke's pouch and courses ventrally. The first notable cerebral branch of the carotid at this stage is the primitive dorsal ophthalmic artery, which now supplies an extensive capillary plexus investing the optic cup. The primary cranial division of the internal carotid gives rise to several branches. The largest of these is the primitive anterior choroidal artery, which supplies the diencephalon in its course to the choroid fissure of the brain. Just distal to this are several twigs representing the middle cerebral stem. Before the cranial division of the carotid terminates at the olfactory pit, it gives off mesial twigs in the path of the future anterior cerebral artery. Opposite the anterior choroidal artery, the carotid supplies a short branch to the more cranial and ventral parts of the optic plexus. This is the primitive ventral (nasal) ophthalmic artery. As will be discussed more fully in a later section of this paper, the arterial supply to the eye remains plexiform until well into the "post-branchial phase" (Congdon), and no single branch of the internal carotid can be traced into the fetal ocular cleft at this stage.

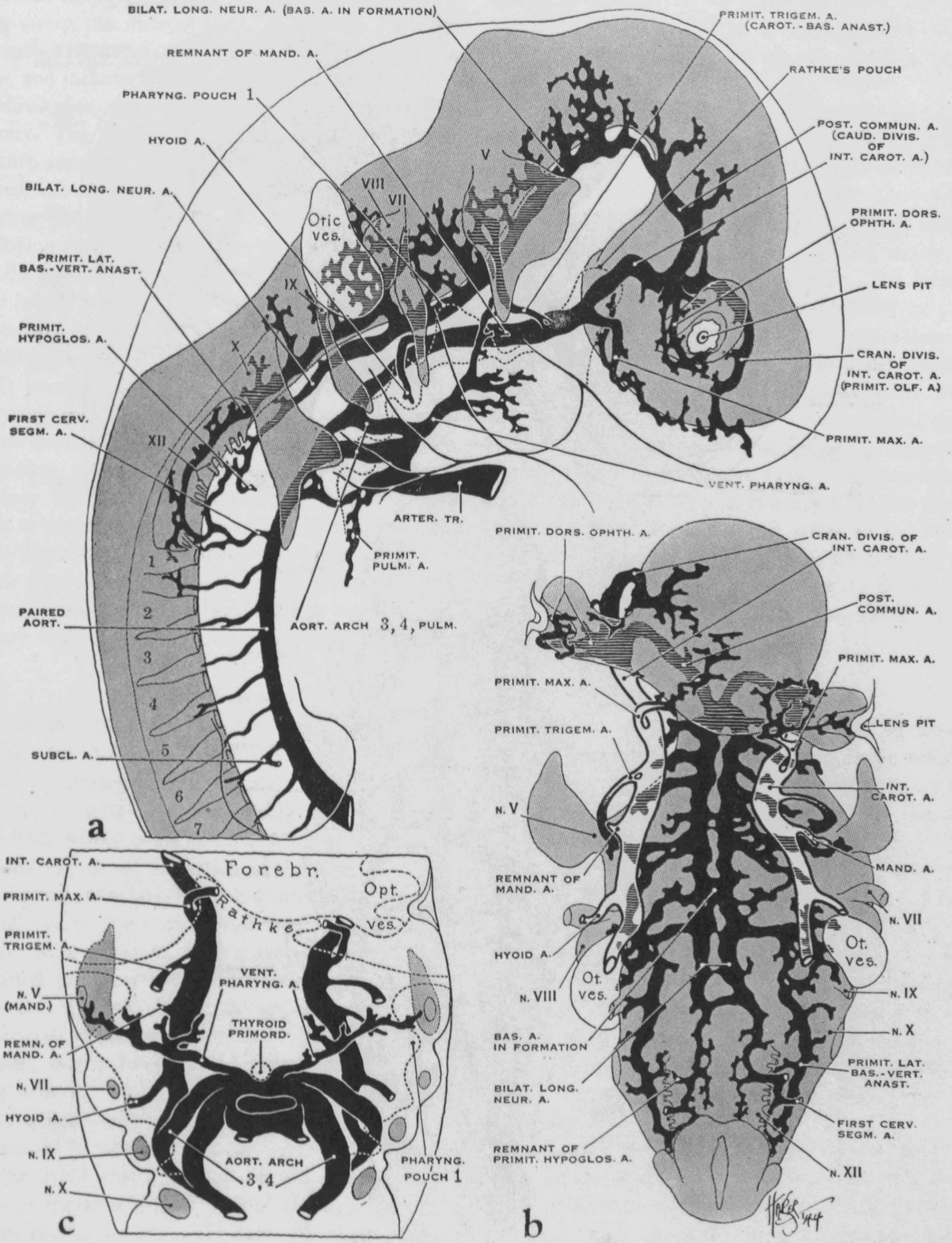

FIG. 3. Stage 2. Right lateral (*a*) and two ventral views (*b* and *c*) of the arteries in a 5.5-mm. embryo (no. 3960) belonging to the same age group as that shown in the preceding figure. Note particularly the persistent primitive trigeminal artery, which is dwindling at the carotid on both sides; the formation of the basilar artery; the large ventral pharyngeal and hyoid arteries, as contrasted with the small remnant of the mandibular artery. Two early stages in arterial supply to the eye are shown on the right and left sides of the embryo, respectively (*b*). ×37.5.

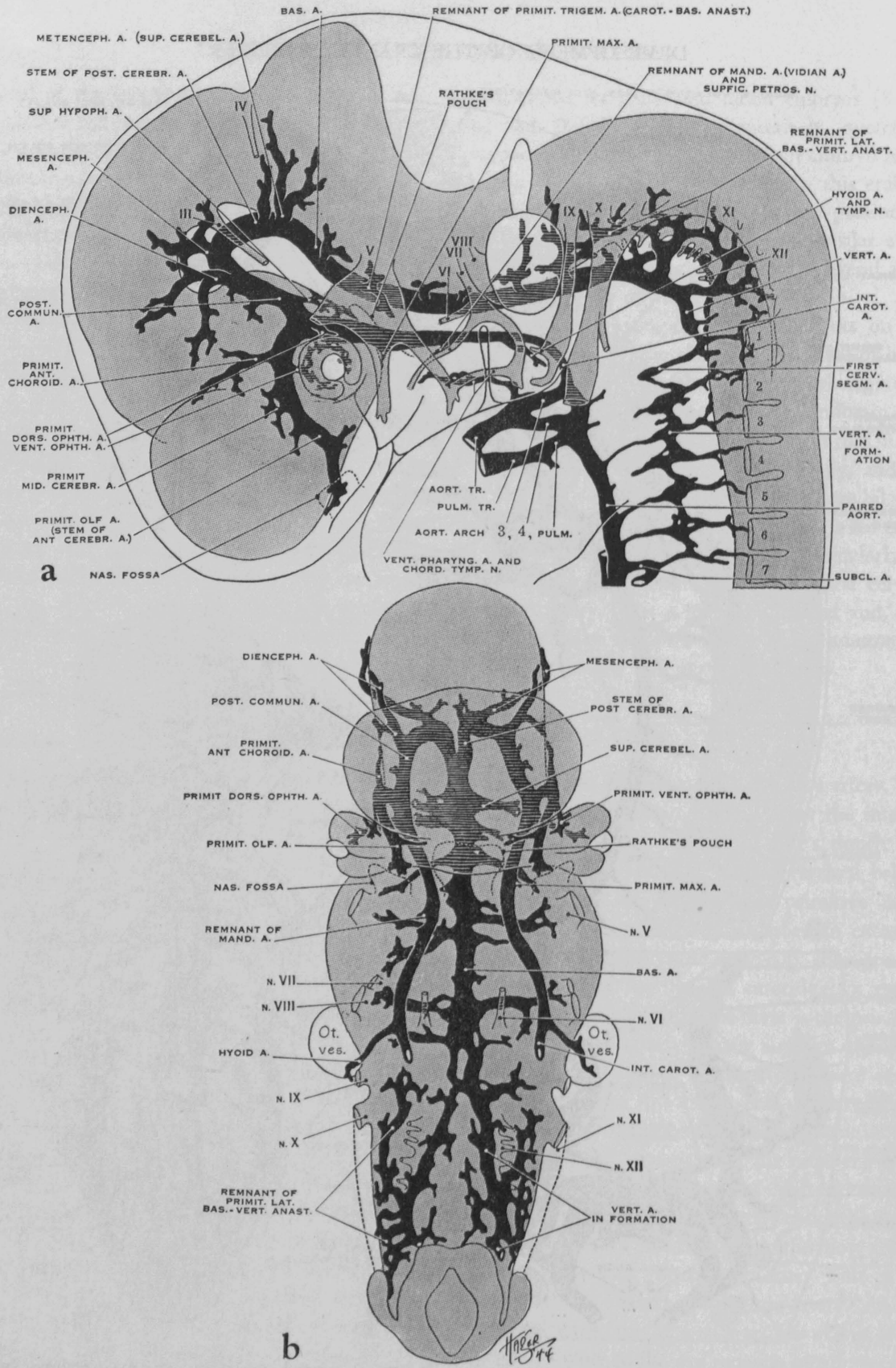

FIG. 4. Stage 3. Lateral view (*a*) of the arteries on the left side of a 9-mm. embryo (no. 163). Note the formation of the vertebral artery from elements of the upper cervical segmentals; the caudal swing of the seventh nerve and its associated hyoid artery; the ventral pharyngeal artery lying against the mandibular end of the chorda tympani nerve; and the two primitive arteries supplying the eye. The primitive olfactory artery (cranial division of the internal carotid) terminates at the nasal fossa. The lower figure (*b*) is a ventral view of a 7-mm. embryo (no. 617) belonging to the same age group as that shown above. ×33.3.

From the caudal end of the posterior communicating artery, just in front of the third nerve, two large branches have emerged. One supplies the diencephalon, and includes a posterior choroidal branch, which is directed toward the domain of the anterior choroidal artery. The other supplies the mesencephalon. The future superior cerebellar artery is now clearly defined, leaving the cranial end of the basilar and supplying the region of the fourth nerve and the developing metencephalon. Caudal to this, the branches of the basilar artery are more or less symmetrical, and are largest at the level of the nerve roots. The most noteworthy feature in the hindbrain region of all these embryos is a lateral channel (or remnants of this channel) paralleling the bilateral longitudinal neural artery as described above in reference to no. 3960 (fig. 3). Now that the basilar and vertebral arteries are almost complete, this channel sometimes constitutes an accessory basilovertebral anastomosis. In its continuous, as contrasted with its partially interrupted, form it is very conspicuous in the 7- and 8-mm. embryos of Elze (1907; see Evans, 1912, fig. 419) and Barniville (1914) respectively. As seen in our embryos, this artery of the hindbrain extends from the level of the otocyst to the first cervical segmental artery, and traverses the area between the sixth and twelfth nerve roots mesially, and the seventh and eleventh roots more laterally.

The basilar artery is irregular and marked by many islands in no. 617, of 7 mm. (fig. 4*b*), but complete in no. 163, of 9 mm. (fig. 4*a*). In the 11.8-mm. embryo (no. 1121; see fig. 45, pl. 5) there are interrupted basilar and carotid remnants of the trigeminal artery which was so conspicuous in the preceding stages; in no. 163 there is a basilar remnant only. The formation of the vertebral artery is well shown in one embryo of this group, no. 163 (fig. 4*a*), where there is a transverse anastomosis between each upper cervical segmental artery and the one adjacent to it. The subsequent obliteration of the proximal or aortal ends of the upper six segmentals is already in progress. As was noted by Congdon (1922), the secondary transverse anastomoses pass caudally from the more proximal end of one segmental artery to the more distal end of the next, so that a significant part of each segmental artery is represented in the completed vertebral, which is zigzag or tortuous in all early stages (compare figs. 4*a* and 5*a*).

Stage 4, Embryos Approximately 12–14 mm., Age Group XVII

This important stage in general development, which marks the transition from "branchial" to "postbranchial" phase (Congdon), shows several more or less obvious advances in the cerebral arteries. Of considerable interest is the fact that it illustrates a fundamental step in the formation of the stapedial artery. As in the preceding stage, individual differences in correlation of size with nervous and arterial development were apparent, and 4 embryos were reconstructed to determine characteristic features of the group as a whole. There are several inconsistencies in arterial development, one feature being more advanced, another less so in one embryo than in another (see table 1). The description which follows, therefore, is necessarily composite, and two embryos are illustrated in figures 5 and 6.

The hyoid artery, with its carotid stem of origin now at the most cranial level of the hyoid bar, has given rise to an important collateral branch which passes through the stapes primordium between the first pharyngeal pouch and the seventh nerve, and descends into the mandibular substance. Below the pharynx, this secondary branch of the hyoid artery has anastomosed with a distal remnant of the ventral pharyngeal artery which lies on the mesial aspect of the mandibular and chorda tympani nerves (fig. 6; fig. 32, pl. 3). In this manner is established the maxillomandibular division of the now definitive stapedial artery. A component of the external carotid artery, often including thyroid and lingual branches, is present and undoubtedly represents the proximal part of the ventral pharyngeal artery (Congdon, 1922). With the approaching obliteration of the segment of paired aorta between the third and fourth aortic arches (drawn out in a thread in no. 1771, fig. 5), the common carotid artery may now be identified.

Considerable advance is apparent in the arteries supplying the eye (fig. 5). The stem of the primitive dorsal ophthalmic artery is elongated and has two optic branches, a common temporal ciliary artery supplying the caudodorsal aspect of the optic cup, and a hyaloid branch penetrating the fetal ocular cleft. The primitive ventral ophthalmic branch of the inter-

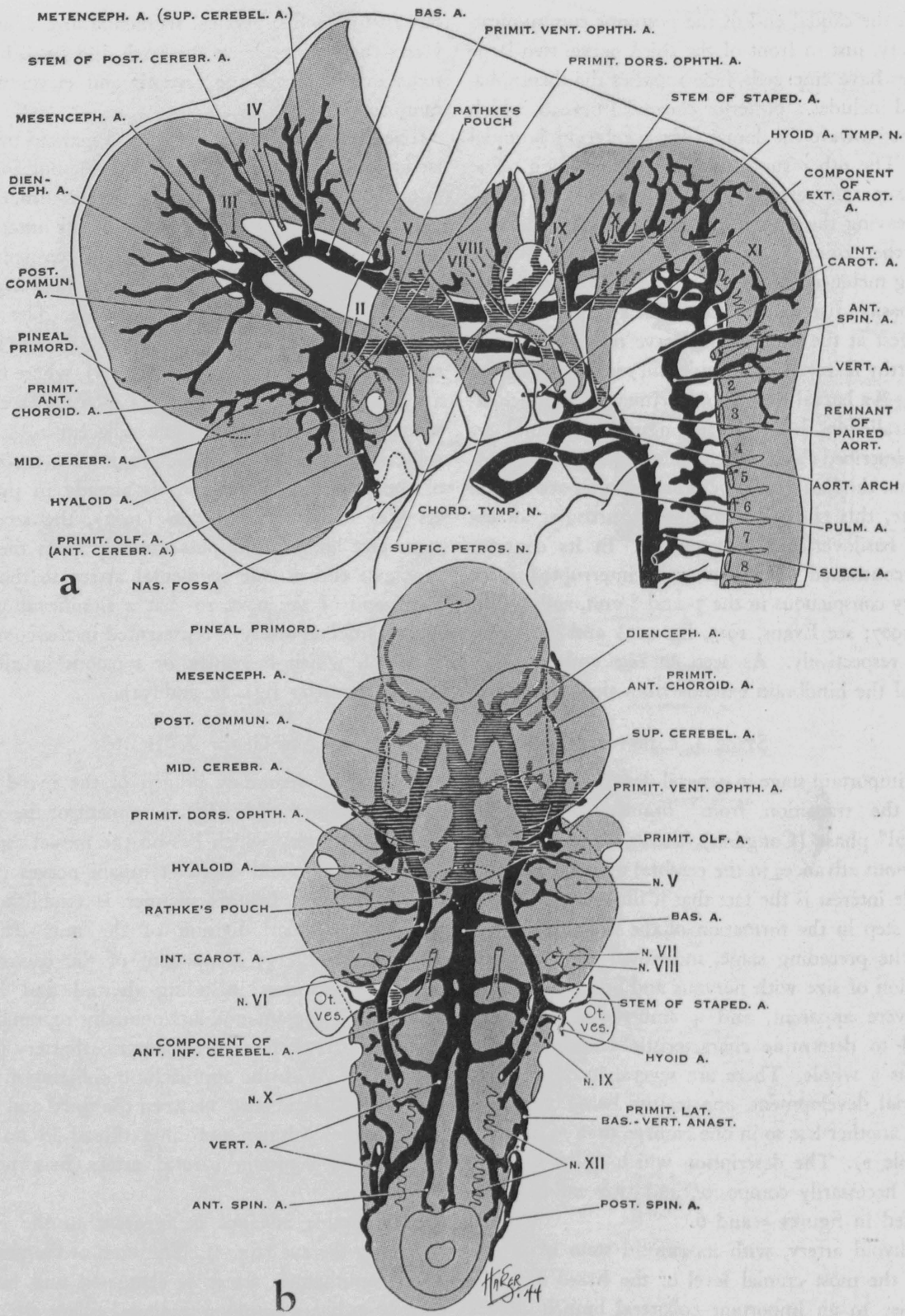

FIG. 5. Stage 4, which ushers in the "postbranchial phase" (see also fig. 6). The cranial arteries in a 12.5-mm. embryo (no. 1771). Developments to be particularly noted are: the new stapedial branch of the hyoid artery, the stem of which has been shifted cranially; the more advanced conformation of the vertebral artery; the emergence of several well defined cerebral arteries; and the elongation and differentiation of the two primitive ophthalmic branches of the internal carotid. ×20.

nal carotid, whose distal part later constitutes the common nasal ciliary artery, is also drawn out in length owing to the beginning elongation of the stalk and ventrolateral shifting of the eye away from the brain wall. It should be noted that the stem of the ophthalmic artery in permanent adult position has not yet appeared.

the situation appears to be the reverse; that is, the middle cerebral appears to be the direct continuation of the carotid artery, with the anterior cerebral as its collateral branch (compare figs. 17 to 21, pl. 1). Another important advance appears at the terminal end of the cranial division of the carotid, which still constitutes a primitive olfactory artery as in all earlier

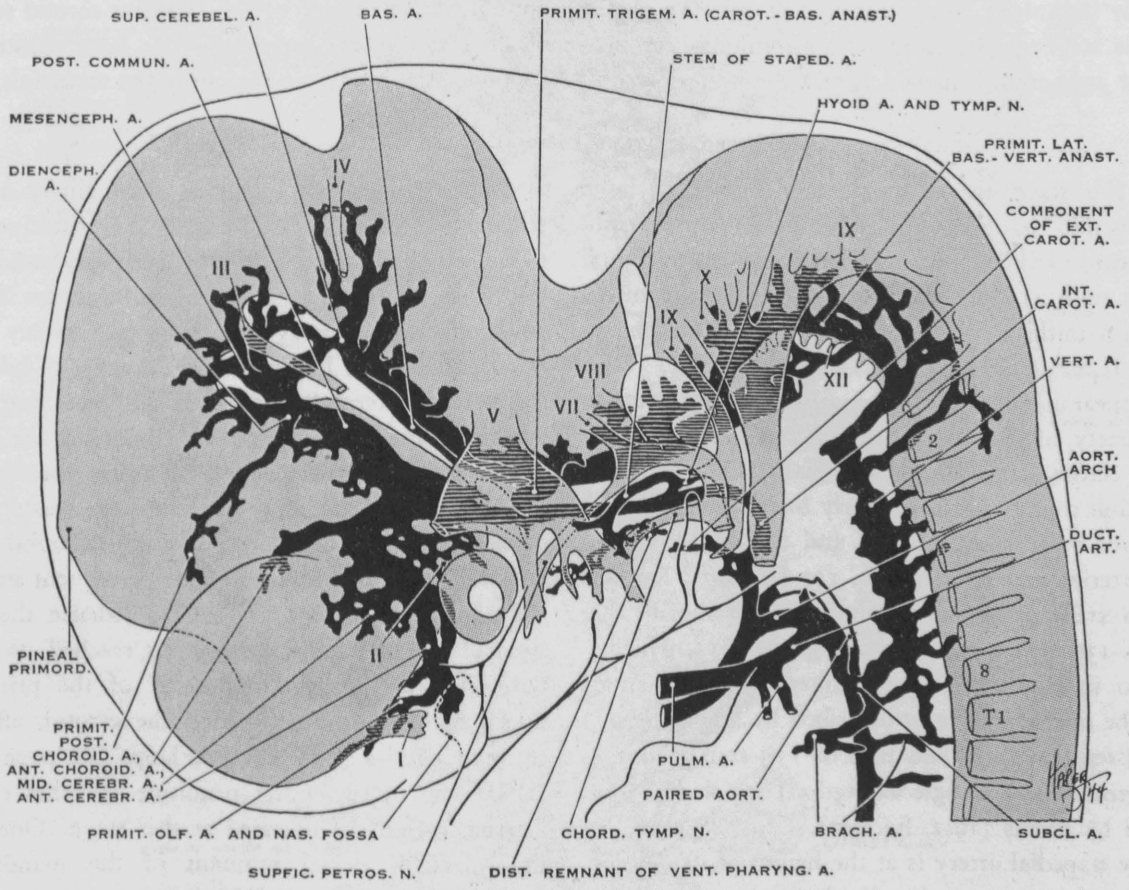

FIG. 6. Stage 4. The cranial arteries on the left side of a 14-mm. embryo (no. 940) belonging to the same age group as that shown in figure 5; although the cerebral arteries are comparatively more primitive—note the persistence of the trigeminal artery (see also fig. 42, pl. 4)—development in general, including that of the aortic arch system, is more advanced. This figure shows the invasion of the mandibular bar by the new stapedial artery, which is a collateral of the hyoid artery. The stapedial has annexed the distal end of the ventral pharyngeal artery, the proximal part of which is now a component of the external carotid. (Details of the stapedial artery supplied from a freehand reconstruction of another 14-mm. embryo, no. 6258.) ×20.

The primary cranial division of the internal carotid may be described for the first time with respect to the definitive parts and collateral branches of the adult conformation. The most proximal segment of this carotid division gives off the anterior choroidal artery as its first branch; the second collateral is the middle cerebral artery, and, with its appearance, the next segment may be named the stem of the anterior cerebral artery. It will be remembered that in the adult

stages (figs. 1–5). It now has two branches, the original one to the nasal fossa and a secondary one passing more mesially toward the emerging olfactory nerve root. The latter artery, which represents the future continuation of the anterior cerebral artery, may be joined during the end of this stage with its fellow of the opposite side by plexiform anastomoses in the mid-line region of the future anterior communicating artery (fig. 46, pl. 5).

Further development of the anterior and posterior choroidal arteries, as well as of the basilar and the vertebral arteries with their branches, is readily seen by comparing figure 5 with figure 4 of the preceding stage. Except in two embryos of 11.5 and 14 mm. (see table 1 and fig. 6), the cerebral arteries are far less plexiform and the origin of many adult arteries is already indicated. The trigeminal artery may persist at this stage in the form of a prominent caroticobasilar anastomosis, in which case the posterior communicating artery is small near its junction with the basilar artery (figs. 40–42, pl. 4). The vertebral artery is still irregular, giving evidence of its mode of origin; and in embryo no. 1771 (fig. 5) its cranial part is typically more advanced than its caudal end. This stage is transitional in regard to a significant feature of arterial development in the higher vertebrates, namely, the change from the exclusive carotid supply of all the cerebral arteries to the later substituted supply of the hindbrain region by the vertebrals.

Stage 5, Embryos Approximately 16–18 mm., Age Groups XVIII, XIX [2]

At this stage, the descent of the heart and large arteries into the thorax is further advanced; the common carotid is thereby elongated, and the vertebral artery, with its subclavian stem of origin now shifted cranially to the adult position opposite the pulmonary arch, is straightened out and fairly regular. With the appearance of the permanent stem of the ophthalmic artery, as well as further differentiation of many other cerebral arteries and external carotid branches, the adult configuration is clearly foreshadowed. Two embryos were reconstructed, and the appearance of the arteries and brain in no. 144 (16 mm., late age group xviii) proved to be almost identical with that in no. 1390 (18 mm., early age group xix), which is shown in figure 7. These embryos are also much like the one of 17.8 mm. described by Thyng (1914) and Bremer (1943) and that of 15.5 mm. (no. 390, age group xix, Carnegie Collection) which was illustrated by Evans (1912, fig. 447).

The stapedial artery is at the height of its development and has two major divisions: the ventral division, which was established in the preceding stage (fig. 6), is the common stem for the mandibular and maxillary (infraorbital) branches; the dorsal or supraorbital division, whose stem appeared in the last stage, now courses lateral to the Gasserian ganglion and far cranially into the primitive orbit. The stem of the ophthalmic artery has finally appeared in adult position, caudal to the optic nerve and lateral to Rathke's pouch, but its domain is limited as formerly to the optic cup and lens. Its three branches are the common temporal ciliary and the hyaloid arteries (branches, during the preceding stage, of the primitive dorsal ophthalmic artery, whose stem has now disappeared) and the common nasal ciliary artery, which represents the distal end of the primitive ventral ophthalmic branch of the internal carotid. At this time, therefore, the components of the future adult ophthalmic artery arise from two widely separated parts of the internal carotid artery, as follows: the orbital arteries come from the most proximal part by means of the supraorbital division of the stapedial artery; the ocular arteries, which temporarily had two separate points of origin from the more distal carotid (the primitive dorsal and ventral ophthalmic arteries), are now branches of the permanent stem of the ophthalmic artery. There is evidence that the stem of the ophthalmic artery has reached its adult position by a caudal "migration" of the primitive dorsal ophthalmic artery along the carotid, effected through a series of anastomotic loops (see page 246).

The fate of two other primitive branches of the internal carotid is indicated at this stage. One may find a small dorsal remnant of the mandibular artery, which accompanies the superficial petrosal (Vidian) nerve skirting the lateral aspect of the carotid. Also seen in some embryos is the small primitive maxillary artery, which is now directed more mesially than ventrally toward the dwindling craniopharyngeal canal along the caudal border of the hypophysis; this becomes a component of the inferior hypophyseal artery. Coincidently with the appearance of the definitive common carotid artery, several external carotid branches may be identified, including the thyroid, lingual, occipital, and external maxillary arteries. The proximal segment of the internal maxillary artery is sometimes seen to extend toward the maxillomandibular division of the stapedial artery, foreshadowing their approaching anastomosis.

This stage shows a noteworthy advance in the ar-

[2] Age group xviii is the oldest group thus far completed in the Carnegie survey. See Streeter (1942, 1945, 1948).

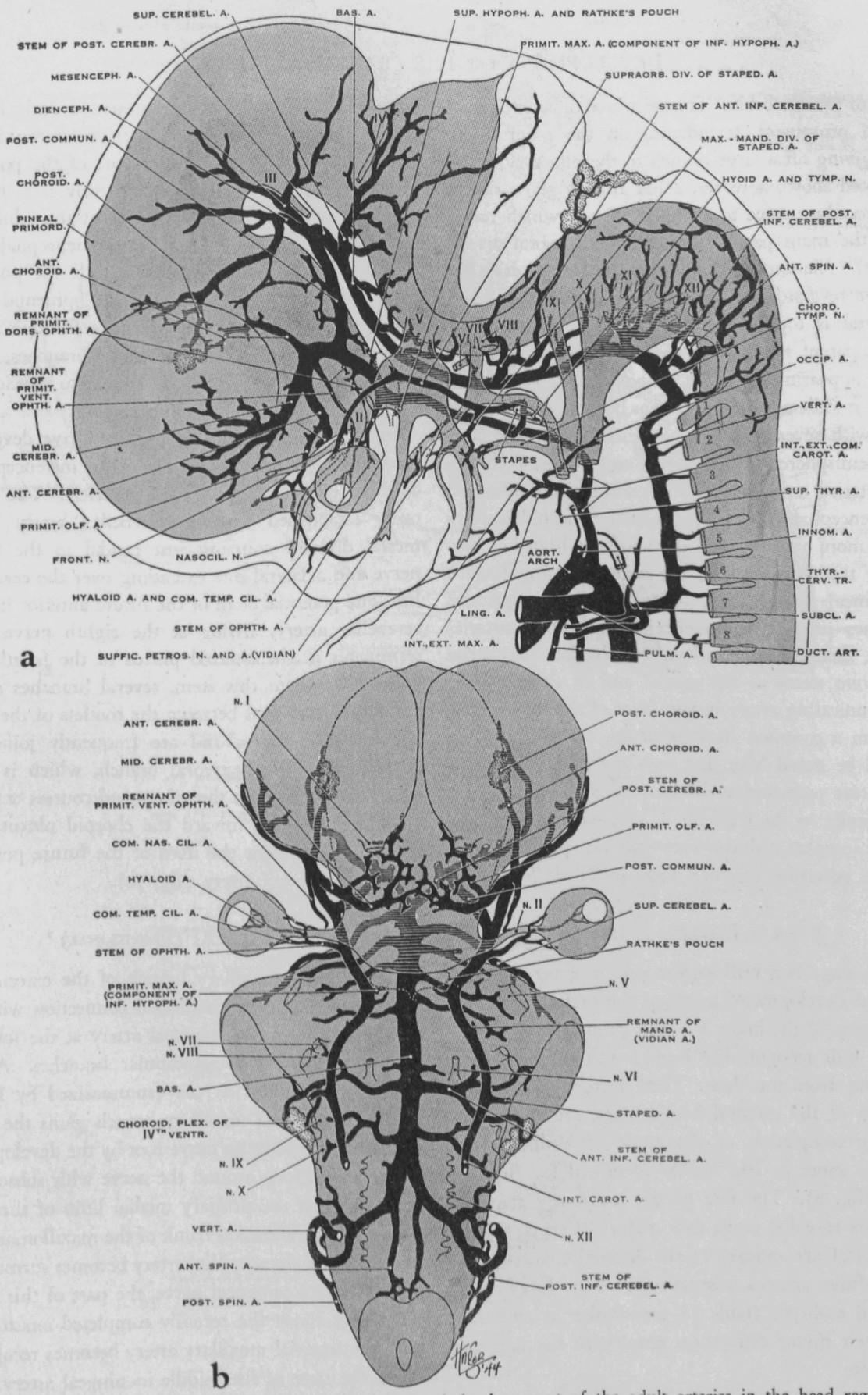

FIG. 7. Stage 5. An 18-mm. embryo (no. 1390) of the period when most of the adult arteries in the head region become recognizable. Note particularly the new adult stem of the ophthalmic artery, which annexes the ocular branches of the primitive ophthalmic arteries (see also fig. 13; fig. 33, pl. 3). The well developed stapedial artery has two major divisions which comprise three branches, mandibular, maxillary, and orbital. ×16.7.

teries of the forebrain. The primitive olfactory artery is still prominent, terminating in the nasal cavity after giving off a large branch to the olfactory nerve. As noted above, however, it has already given rise in the preceding stage to a mesial branch which represents the main part of the anterior cerebral artery. Now the relation of primary to secondary arteries has become reversed, so that the mesial anterior cerebral collateral is topographically the direct continuation of the parent artery, with the more lateral olfactory artery appearing to be its branch.

The middle cerebral artery has become a prominent stem with several branches spreading over the cerebral hemisphere. Both anterior and posterior choroidal arteries terminate in the choroidal infolding at the diencephalic roof. The posterior choroidal artery is the more anteroventral of two large branches supplying the diencephalon, the other coursing toward the pineal primordium. Two equally conspicuous branches supply the mesencephalon. These arteries to the diencephalon and mesencephalon may arise from two stems at the caudal end of the posterior communicating artery just in front of the third nerve, or from a common stem as in no. 1390 (fig. 7). It should be noted here that only the first segment of the future posterior cerebral artery is represented unequivocally in the embryos of this series. De Vriese (1905) emphasized the fact that the proximal end of the posterior cerebral (the so-called "divisional branch of the basilar") is represented early by the most caudal segment of the posterior communicating artery, from which the greater part of the posterior cerebral arises as a collateral relatively late in fetal development. It will be recalled that the adult posterior cerebral gives off several small diencephalic and mesencephalic branches which include the posterior choroidal artery (fig. 11*a*). The developmental emergence of the posterior cerebral artery, through an enlargement of one of this group of branches, when the cerebral hemispheres have begun to envelop the midbrain, may be readily imagined.

The branches of the basilar artery have developed parallel with the differentiation of the metencephalon and the region of the fourth ventricle. The previously established superior cerebellar artery has a mesial division coursing just caudal to the fourth nerve and a lateral one extending over the cerebellar lip. The potential stem of the future anterior inferior cerebellar artery, arising at the eighth nerve level, terminates in the choroid plexus of the fourth ventricle. Caudal to this stem, several branches of the vertebral artery pass between the rootlets of the tenth and eleventh nerves and are frequently joined by anastomoses. One vertebral branch, which is often more prominent than the others and courses cranially along the medulla toward the choroid plexus, may be said to represent the stem of the future posterior inferior cerebellar artery (fig. 7*a*).

Stage 6, Embryos Approximately 20–24 mm., Age Groups XX, XXI (Provisional) [3]

This stage is a well known one in general craniocerebral development, marking the period when the curvatures of the brain are most pronounced and the head, with recognizably human features, begins to lift away from the chest. These factors, plus the expansion of the cerebral hemispheres, are responsible for the completion of the circle of Willis, which may be more or less readily identified for the first time (fig. 8). The fate of the temporary stapedial artery is revealed as its two major divisions, ventral and dorsal, are annexed by the internal maxillary and ophthalmic arteries respectively. The four reconstructed embryos (table 1) are similar in essentials, and their minor differences emphasize the sequence of events.

The internal maxillary branch of the external carotid artery has now established connection with the lower division of the stapedial artery at the junction of its maxillary and mandibular branches. As described by Tandler in 1902 (summarized by Evans, 1912), the internal maxillary branch gains the outer side of the mandibular nerve root by the development of an arterial loop around the nerve with subsequent obliteration of the primary medial limb of the loop. As soon as the common trunk of the maxillomandibular division of the stapedial artery becomes surrounded by the auriculotemporal nerve, the part of this trunk which lies above the recently completed anastomosis with the internal maxillary artery becomes recognizable as the stem of the middle meningeal artery. The supraorbital division of the stapedial artery, in the

[3] See footnote 2.

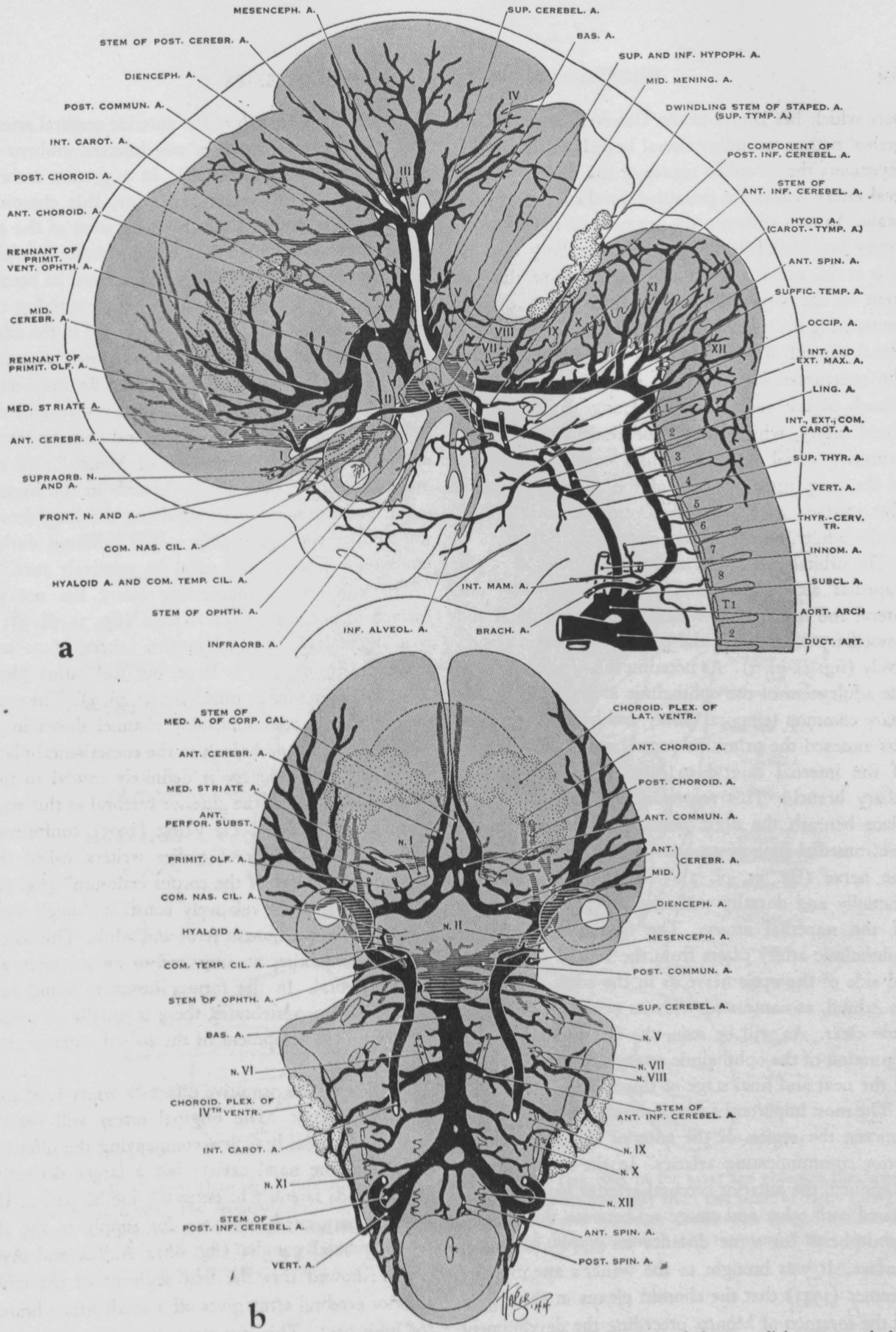

FIG. 8. Stage 6. A 24-mm. embryo (no. 632, injected). Note (*a*) the dwindling stem of the stapedial artery and the two secondary anastomoses by which its major divisions are annexed by, respectively, the ophthalmic artery to form its orbital branches, and the internal maxillary artery to form the stem of the middle meningeal artery. The anterior communicating artery completes the circle of Willis (*b*). Derivatives of the primitive olfactory artery now penetrate the anterior perforated substance as striate branches of the anterior cerebral artery. ×13.3.

part which lies lateral to the Gasserian ganglion, together with a secondary dorsal branch of this artery, represents the extended course of the middle meningeal artery within the primitive dural covering of the brain. In two embryos, the segment of the stapedial artery just mesial to the stapes is dwindling (fig. 9). It is at this point, not at the internal carotid, that the stem of the stapedial artery is interrupted, thereby transposing the two lower stapedial branches to the external carotid artery. The remaining distal part of the interrupted stapedial stem becomes the tympanic branch of the adult middle meningeal artery. The hyoid artery, which, it will be remembered, is the primitive vessel which has just served temporarily as the most proximal part of the stapedial stem, is also retained as the small caroticotympanic branch of the adult internal carotid artery (fig. 8*a*).

The orbital end of the supraorbital division of the stapedial artery has developed two branches, one lateral and one medial, which follow the frontal and nasociliary branches of the ophthalmic nerve, respectively (fig. 34, pl. 3). As noted in the preceding stage, the adult stem of the ophthalmic artery, with its primary common temporal ciliary and hyaloid branches, has annexed the primitive ventral ophthalmic branch of the internal carotid to form its common nasal ciliary branch. This secondary anastomosis, taking place beneath the optic nerve, now constitutes the ventromedial limb of an arterial ring which encircles the nerve (fig. 35, pl. 3). This loop is connected cranially and dorsally with the supraorbital division of the stapedial artery. The means whereby the ophthalmic artery passes from the ventral to the dorsal side of the optic nerve as in the adult, and gains its orbital, as contrasted with its ocular, branches, is now clear. As will be seen, the essential adult configuration of the ophthalmic artery becomes definitive at the next and final stage of this series.

The most important advances in the cerebral arteries concern the region of the anterior cerebral and anterior communicating arteries. In the four embryos examined, the anterior cerebral arteries have approximated each other and course up between the cerebral hemispheres for some distance to supply its mesial surface. It was brought to the writer's attention by Bremer (1943) that the choroid plexus in the region of the foramen of Monro, preceding the development of the corpus callosum from the commissural plate, is supplied by a branch of the anterior cerebral artery. This branch was noted in our injected embryo of 24 mm. (fig. 8*a*, not labeled). In a 39-mm. embryo (no. 6203) of the succeeding stage, this choroidal branch is less direct; since the main stem of the anterior cerebral artery has been drawn farther cranially and dorsally by the expanding hemisphere, its branch loops caudally for some distance before entering the choroid plexus. Shellshear (1930*b*) found in the adult chimpanzee (whose cerebral arteries closely resemble those of man) a fine vessel, continuing the main stem of the anterior cerebral, which recurves around the splenium into the third ventricle and "can be traced as far forward as the foramen of Monro." No example is known of a similar branch in the human adult, and instances of its surviving the long detour imposed by the intervening corpus callosum during embryonic development must be relatively rare.

The anterior communicating artery has not yet formed in one embryo of 21 mm. (fig. 34, pl. 3); it is a single large channel in two others, of 21 and 23 mm. (fig. 9), and is large, but still rather plexiform, in no. 632, of 24 mm. (fig. 35, pl. 3). The completed anterior communicating channel shows in all cases a well marked branch to the commissural plate; the course of the artery is definitely caudal to that of the main stem of the anterior cerebral at this stage (fig. 8*a*, not labeled). De Vriese (1905), conforming with the terminology of earlier writers, called this the "median artery of the corpus callosum" (fig. 8*b*) and found it to be relatively constant though varying in size in the human fetus and adult. This artery may become either an unpaired or an accessory anterior cerebral. In the former instance, found normally in many vertebrates, there is usually an associated lack of development of the paired anterior cerebral arteries.

The fate of the primitive olfactory artery is of considerable interest. The original artery still persists as a small mesial branch accompanying the olfactory nerve into the nasal cavity; but a larger derivative now extends laterally to enter the mesial part of the anterior perforated substance for supply to the developing basal ganglia (fig. 8*b*). Aitken and Ayer (1909) showed that the first segment of the adult anterior cerebral often gives off a small striate branch (or branches). This inconstant branch, varying considerably in size, obviously represents the stem of the

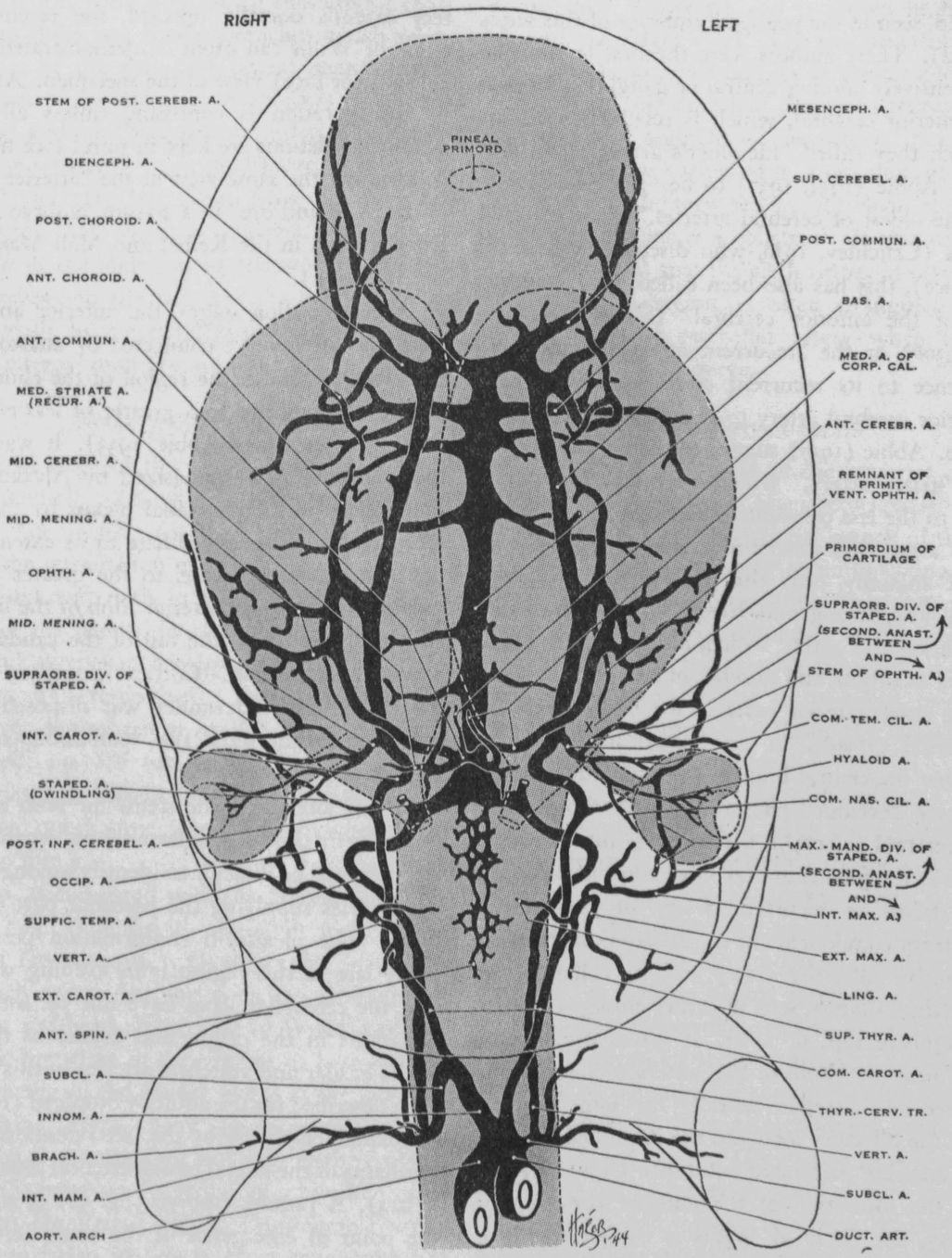

FIG. 9. Stage 6. Coronal (face view) reconstruction of a 23-mm. embryo (no. 966) of the same age group as that shown in the preceding figure. The recently completed circle of Willis can usually be seen only from this point of view, owing to the extreme cerebral curvatures of the 20-mm. stage (compare fig. 8). The two secondary anastomoses formed by branches of the stapedial artery (its stem interrupted in the preceding embryo and dwindling here) with the stem of the ophthalmic artery and with the internal maxillary artery are well shown. ×16.7.

primitive olfactory artery (fig. 7), that is, the terminal part of the cranial division of the primitive internal carotid, seen in the youngest embryos of this series (figs. 1, 2). These authors were the first to describe comprehensively another central or ganglionic branch of the anterior cerebral, which is relatively constant and which they called "Heubner's artery"; this was noted by Abbie (1934, 1937) to be "phylogenetically one of the oldest of cerebral arteries." As confirmed by others (Critchley, 1930, who discusses its clinical significance), this has also been called the "recurrent branch of the anterior cerebral" (Shellshear, 1920, 1930*a*, 1930*b*) or the "recurrent artery of Heubner" in reference to its recurrent course laterally along the anterior cerebral artery to the anterior perforated substance. Abbie (1937) suggested the definitive term "medial striate artery," which may also be applied properly to the less constant remnant of the primitive olfactory artery just described. Among leading textbooks of anatomy, only the 1944 edition of Gray's *Anatomy* and Strong and Elwyn's 1943 *Neuroanatomy* mention this artery which, although variable in size, point of origin, and number of branches, supplies the more anteroinferior parts of the corpus striatum and internal capsule. It was noted by Alexander (1942) that the central branches of the adult anterior cerebral are developed reciprocally with those of the middle cerebral artery; in the 20- to 40-mm. embryos (figs. 8, 10) the former are far more conspicuous. The medial striate or recurrent artery of Heubner is formed from components of the anastomosis between the primitive olfactory artery and its collateral anterior cerebral branch, seen in earlier embryos (fig. 34, pl. 3; compare figs. 6, 7, 8). It leaves the anterior cerebral near or opposite the anterior communicating artery and extends laterally for some distance between the olfactory lobe and the brain before entering the anterior perforated substance (figs. 8–11).

With the formation of the anterior communicating artery, the circle of Willis is completed. It is, however, seldom readily recognizable in the ventral or base view of the embryo, because of the exaggerated cerebral curvatures of the 20-mm. stage. The posterior communicating artery, which at first proceeded cranially from the carotid to the basilar artery and appeared to be a direct continuation of the carotid, is gradually swung upward and finally backward as on a hinge, and ultimately leaves the carotid at an angle of approximately 90°. At the 20-mm. stage, when the posterior communicating artery extends dorsally upward, the recently formed circle of Willis can often be demonstrated only by a coronal (or face) view of the specimen. As thus seen, its configuration is confusing unless all the topographical relations are kept in mind (see fig. 9, which is obviously the same view as the "arteries at the base of the skull and eye" in a 20-mm. embryo reproduced from Versari in the Keibel and Mall *Manual,* vol. 2, fig. 180, 1912).

As in preceding stages, the anterior and posterior choroidal arteries are connected by anastomoses over the diencephalon in the region of the choroid plexus, a condition retained to a greater or less extent in the adult (Beevor, 1909; Abbie, 1933). It was shown by these authors and emphasized by Alexander (1942) that supply to the choroidal plexus by the adult anterior choroidal is subordinate to its extensive central distribution, for instance, to the greater part of the globus pallidus and posterior limb of the internal capsule, the optic tract, the tail of the caudate, and the amygdaloid nucleus. Cortical branches supply the uncinate gyrus. Alexander was disposed to rename the anterior choroidal the "pallido-hippocampo-capsular artery."

At this late stage, the stems for both anterior and posterior inferior cerebellar arteries, especially the latter, may still be difficult to identify among the numerous arteries supplying the posterior part of the hindbrain. The plexiform conformation persisting relatively late in this region is in keeping with the fact that the cerebellar lobes have not yet formed. Wide variations in the origin and course of the branches of the basilar and vertebral arteries in this region have been described for the adult by Stopford (1916). These are explained chiefly by the late retention of different remnants of the lateral basilovertebral anastomosis (see p. 214). A 12-mm. embryo (fig. 5*b*) of stage 4, when the point of emergence of the sixth nerve from the hindbrain is well caudal to that of the seventh and eighth nerves, explains the origin of one type of variation. (A duplicate of this arterial configuration was shown for the adult echidna by Shellshear, 1930*a*, his fig. 1.) Here the sixth nerve is bounded by a closed vascular ring composed of the following: mesially, the basilar artery; cranially, a basilar branch passing dorsal to the nerve and terminating at the

seventh and eighth nerves just ahead of the otocyst; caudally, another basilar branch to the ninth nerve behind the otocyst; and laterally, an anastomotic channel between these two basilar branches which represents a part of the primitive lateral channel mentioned above. If the lateral anastomosis is obliterated, the internal auditory and anterior inferior cerebellar arteries arise separately from the basilar, as shown in figures 10*b* and 11*b* (left side). Loss of the cranial segment is the most common outcome, owing to the cranial shift of the abducens in relation to the facial-acoustic nerves and the fact that the arteries are attracted caudally by the enveloping cerebellum. This leaves the internal auditory artery as a branch of the anterior inferior cerebellar (62 per cent of cases, Stopford) which passes ventral to the sixth nerve (about 75 per cent, Stopford) and is shown in figures 7*b*, 8*b*, and 11*b* (right side). The less frequent instances in which the anterior inferior cerebellar and its auditory branch pass dorsal to the nerve represent a loss of the caudal segment of the original vascular ring or, as Shellshear expressed it, a retention of the original internal auditory artery, of which the anterior inferior cerebellar is a collateral. It was reported by Cushing (1910) that the sixth nerve, in cases of brain tumor in this region, is often strangulated by the anterior inferior cerebellar artery when the artery lies ventral to the nerve.

Stage 7, Embryos of Approximately 40 mm. and Adult Configuration

In the final stage of this series, the adult stem of origin of essentially all the head arteries can be readily identified. The relative size and direction of many as well as the termination of others, notably the posterior cerebral and both inferior cerebellar arteries, remain to be determined by the predominance of the cerebral and cerebellar hemispheres over the brain stem and medulla respectively. Two embryos of different lengths, but otherwise similar, were graphically reconstructed; no. 886 (43 mm.) illustrates general characteristics, and certain important details, particularly of the ophthalmic artery, were supplied by no. 6203 (39 mm.).

Figure 10, as compared with the preceding embryonic stage (fig. 8) and with the adult form shown in figure 11 (see also pls. 1, 2), shows the arterial advances which are in keeping with the development of the brain and head. The circle of Willis is readily seen for the first time in the ventral or base view of the brain, owing to the caudal swing of the posterior communicating artery. Note the large size of this artery, which is characteristic not only of the embryo, but also of the newborn (over half of a hundred cases, according to De Vriese, 1905). Considerable asymmetry and variation in size is often encountered in the posterior communicating artery of the newborn and adult, and also in the divisional branch of the basilar (that is, the first part of the adult posterior cerebral, representing the original caudal end of the embryonic posterior communicating artery, which terminates in the basilar; fig. 11*b*). The posterior cerebral is not infrequently given off from the internal carotid in the position of the posterior communicating artery, a variation often accompanied by small size of the connecting divisional branch of the basilar. The typical adult posterior communicating artery is small, of a caliber a little larger than that of the anterior choroidal artery, according to De Vriese. The diminished size of the vessel is the result of the transfer of the blood flow of its posterior cerebral collateral, which forms late, from the carotid to the basilar and vertebral system.

Figure 11, showing the cranial arteries in the newborn, illustrates aspects of adult configuration which are inadequately or incorrectly depicted and described in many textbooks of anatomy. Note particularly (11*b*) that the origin of the anterior cerebral, which is usually dorsal in the adult and, therefore, hidden from below by the parent internal carotid, is just distal to the anterior choroidal artery, although many current illustrations show it arising opposite or even proximal to the posterior communicating artery. The median artery of the corpus callosum, which is often well developed at term (De Vriese, 1905), sometimes constitutes an accessory or median anterior cerebral. The greater part of the relatively constant medial striate artery is usually hidden by the parent anterior cerebral when the adult circle of Willis is viewed *in situ*. The superior hypophyseal arteries, which are ordinarily very small, are exaggerated in the accompanying illustration, and the inferior hypophyseals from the intracavernous part of the internal carotid are not shown. Note the variable origin of the two inferior cerebellar arteries, which are formed much

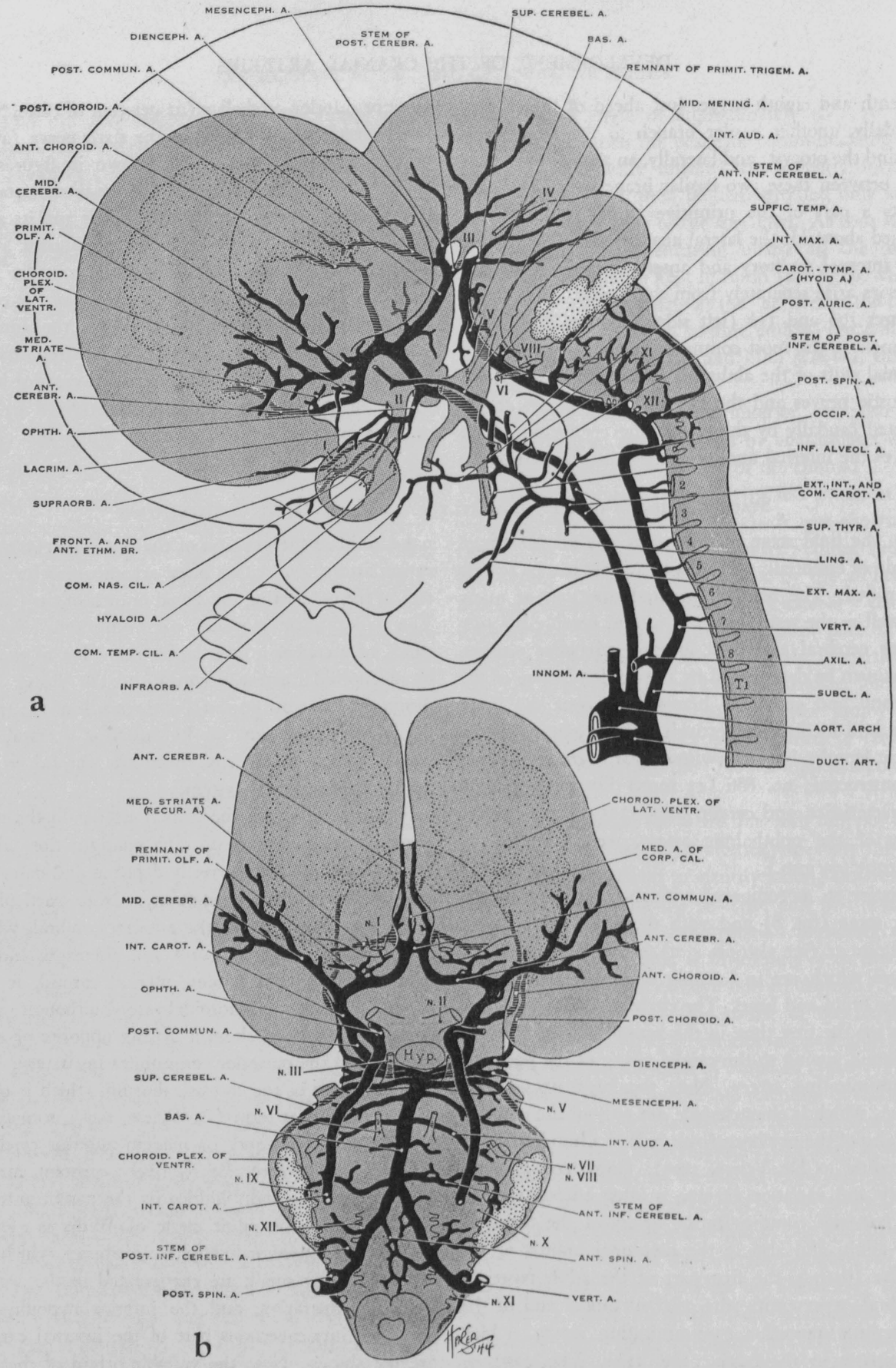

FIG. 10. Stage 7. A 43-mm. embryo (no. 886); details supplemented by reconstructions of no. 6203, 39 mm. Although the embryos are less than two months old, their cranial arteries are readily comparable to those of the adult. Further extension of the posterior cerebral and both inferior cerebellar arteries awaits only the future predominance of the cerebral and cerebellar hemispheres. The ophthalmic artery is complete, having incorporated part of the supraorbital division of the stapedial artery as its lacrimal branch. The definitive middle meningeal artery and essentially all external carotid branches are present. ×6.7.

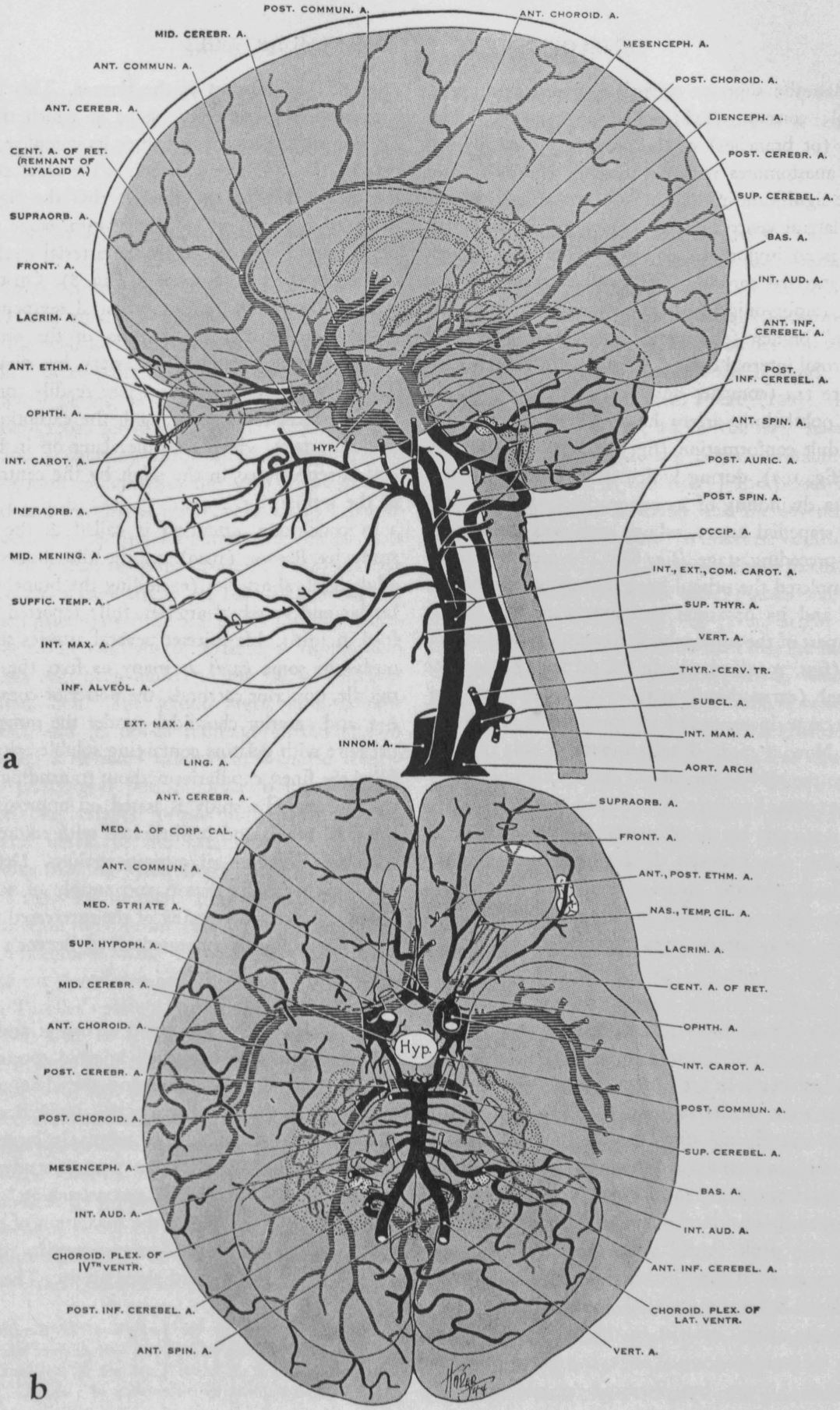

FIG. 11. The newborn configuration, which is essentially the same as that of the adult, although there is typically less relative difference in the size of the arteries composing the circle of Willis and those immediately derived from it. See page 227 for the details to be noted in this figure.

later than the superior cerebellar, whose position is relatively constant (11*b*). The posterior choroidal branch (or branches) of the posterior cerebral commonly anastomoses with the anterior choroidal, and is more significant in the supply of the choroid plexus of the lateral ventricle than is the anterior choroidal, which is an important central or ganglionic branch of the internal carotid. The small caroticotympanic branch (embryonic hyoid artery) and, above it, the "Vidian" branch (embryonic mandibular artery) of the petrosal internal carotid are shown but not labeled in figure 11*a* (compare figs. 7, 8, 10).

The ophthalmic artery has attained the approximate adult conformation (fig. 11*a, b*) in the 40-mm. stage (fig. 10*a*), during which time there is either a loss or a dwindling of its connections with the temporary stapedial artery, whose stem was interrupted in the preceding stage (fig. 8). The lacrimal artery has completed the orbital branches of the ophthalmic artery, and its proximal end represents the strictly orbital part of the supraorbital division of the stapedial artery (figs. 35, 36, pl. 3). In the preceding stage, the proximal (extraorbital) part of this stapedial division became incorporated in the middle meningeal artery. Now, a more distal segment of this division, between the middle meningeal and ophthalmic (lacrimal) arteries, has been interrupted just outside the orbit. As noted by many anatomists, an anastomosis of variable size between the lacrimal branch of the ophthalmic and the anterior branch of the middle meningeal arteries is often found in the adult; sometimes the latter artery gives origin to many or even most of the branches of the former. This is a persistence of the embryonic stage at which the upper division of the stapedial, before its complete annexation by the ophthalmic artery, is the chief supply of the orbit. It is also of interest that the right optic nerve of one embryo of the 40-mm. stage (fig. 36, pl. 3) is still surrounded by the arterial circle which formed in the preceding stage (fig. 8). On the other side of this embryo, a cranioventral segment of this circle, actually the root portion of the secondarily formed common nasal ciliary artery, has disappeared. This leaves the ophthalmic artery readily comparable to the typical adult form, with the exception of the hyaloid artery, which dwindles later on in fetal life, and is represented in the adult by the central artery of the retina (fig. 11*a*).

In conclusion, attention is called to the detailed study by Beevor (1909) on the distribution of the adult cerebral arteries (excluding the branches of the basilar and vertebral arteries, fully reported by Stopford in 1916). He injected several arteries simultaneously—in some cases as many as five, the anterior, middle, posterior cerebrals, the posterior communicating, and anterior choroidal—under the same gradual pressure with gelatine containing soluble colors which filled the finest capillaries without transuding through the tissues. His study is based on approximately a hundred brains and is illustrated with colored photographs of representative brain sections. Details concerning the configuration and supply of several arteries reported since, many of them referred to above, have essentially corroborated all of Beevor's findings.

THE STAPEDIAL ARTERY

Tandler (1902) reported in detail on the development of the stapedial artery in the rat, and described certain late stages in the human embryo. He showed how the stem of the stapedial is taken over by the external carotid, including its role in the formation of the middle meningeal artery, but failed to reveal how it is formed in man. Fuchs (1905), in an exhaustive study of orbital vascular development in the rabbit, also dealt briefly with the stapedial artery, including early stages. Furthermore, he showed the part played by its supraorbital division in the formation of the orbital arteries in this species. Congdon (1922) was not concerned with the development of the stapedial artery, but discussed the relation of the second aortic arch to its stem of origin and pointed out that only especially well injected specimens can be relied upon for determining the changes in vascularization connected with the involution of the first two aortic arches. The relatively large number of embryos available for the present study, particularly as revealed by graphic reconstruction,[4] has clarified the factors leading to the formation of the stapedial artery and has also demonstrated its role in the development of the ophthalmic artery. The stapedial

[4] Vascular changes in the background of formation of the stapedial artery are dependent on several relevant changes in the whole embryonic head, which could not be demonstrated within the limitations imposed by construction of a model.

artery is retained prominently in the adult rat, as is generally known through Evans' review (1912). A fundamental difference in the evolution of the artery in the rabbit was found to resemble closely that in man. In both species the stapedial is a temporary embryonic vessel.

Development of the Stapedial Artery in Certain Vertebrates

The stapedial artery is of considerable interest as an instance of supply to one region of the young embryo head, the mandibular bar (arch) and parts cranial to it, by an artery belonging to another region, namely, the well defined hyoid bar. This phenomenon, which takes place during the emergence from the branchial period, is described in simplest terms by Tandler (1902) for the rat. By the time the third, fourth, and pulmonary aortic arches are completed in the 3.5-mm. rat embryo, the second has already dwindled and the first is interrupted, though prominent vessels representing its dorsal and ventral ends persist. The dorsal remnant of arch I [5] (mandibular artery) traverses the mandibular bar, after giving rise to a branch passing over the oral cavity into the maxillary process. In embryos of 5 mm., a supraorbital branch has also been added to the dorsal remnant of the first arch. The second aortic arch is now interrupted, and its dorsal remnant (hyoid artery) has assumed a deviated caudoventral course behind the first pharyngeal pouch. Since the position of the developing stapes primordium is somewhat cranial and dorsal to the first pharyngeal pouch, it is obvious that the hyoid artery can supply it only through a secondary branch. This stapedial collateral has appeared in the 6.5-mm. embryo and passes cranially to anastomose with the primary mandibular branch of the dorsal remnant of the first arch. The model in Tandler's plate 4, figure 13 shows the dorsal remnant of arch II (hyoid artery) and its recent stapedial branch in their respective positions, caudal and cranial to the first pharyngeal pouch, a configuration which is essentially that of an analogous stage in the embryos of both rabbit and man.

The dorsal end of the first (mandibular) aortic arch is obliterated proximal to its three branches in a subsequent stage which completes their annexation by the stapedial branch of the second (hyoid) arch. Eventually, the mandibular branch of the stapedial artery is largely taken over by the external carotid artery through another secondary anastomosis. The stapedial artery persists, however, in the adult rat as a prominent branch of the internal carotid, retaining its maxillary and supraorbital branches and also contributing to its former mandibular branch.

In the rabbit, according to Fuchs (1905), the stem of the stapedial artery, as in the rat, arises as a secondary branch from the dorsal remnant of the second aortic arch (hyoid artery) and passes forward between the tympanic cavity and the seventh nerve into the mandibular bar. In marked contrast with the situation in the rat, however, the remnant of the dorsal end of the first aortic arch (mandibular artery) has dwindled without having given origin to any branches. At the time of its obliteration, the mandibular and hyoid bars are largely supplied by what Fuchs called the "external carotid" or "ventral remnant of the first two aortic arches." This vessel, as described and illustrated in sections of the rabbit embryo, is definitely homologous to Congdon's "ventral pharyngeal artery" in man. The so-called external carotid of this stage in the rabbit gives off a sizable branch ("Oberkieferast"; see Fuchs' figs. 32, 33, pls. 11, 12) into the lateral maxillary region, and it is with this vessel that the newly formed stem of the stapedial artery makes an anastomosis. As Fuchs expressed his findings in contrasting the rabbit with the rat, the stapedial gains its branches not by annexation of a dorsal "rest" of the first aortic arch, but from "peripheral branches of the external carotid," representing ventral remnants of the first two arches. Although Congdon's discussion has modified the terminology and interpretation of the arteries involved, this manner of formation of the stapedial artery was found to be essentially that of the human embryo.

Unlike that in the rat, the supraorbital branch of the stapedial artery in the rabbit arises, not in common with the other two stapedial branches, but as a derivative of the maxillary branch ("Oberkieferast"). This "bulbo-orbital" artery gains an important role in the rabbit, giving origin to all the orbital arteries and largely annexing even the ocular branches of the

[5] Although Congdon (1922) argued against the advisability of use of the term "arch" for the vessels seen during the involution of the first two aortic arches, the nomenclature of the writers quoted is used in these reviews, with revised terminology in parentheses.

internal ophthalmic artery with the exception of the central artery of the retina. Ultimately, the three branches of the stapedial artery are all taken over by the external carotid, and the stem of the stapedial is interrupted near its origin from the internal carotid.

Grosser, cited by Tandler, Fuchs, and Evans, refers to a variation found in a bat embryo (fig. 34 of Tandler, 1902) in which the stapedial artery gives rise to only mandibular and supraorbital branches. An infraorbital (maxillary) branch, identified as a dorsal remnant of aortic arch I (mandibular artery), is present as a separate derivative of the internal carotid artery. It arises cranial to the stem of the stapedial artery, at the point where the carotid is in contact with the superficial petrosal (Vidian) nerve and follows the nerve to reach the maxillary branch of the fifth nerve. This so-called "Vidian artery" occurs in many adult reptiles, according to Evans, and is of interest in connection with observations on the human embryo to be described below.

Formation of the Stapedial Artery and Its Branches in Man

It is suggested by Evans (1912) that "in man the three branches of the stapedial artery, instead of being derived from the dorsal end of the first [aortic] arch [as in the rat], are probably derivatives of the ventral portion of that arch." This study essentially bears out his statement. Congdon (1922) claimed that the "arch" components Tandler described as taking part in stapedial formation were to be regarded not as late stages of, but rather as vascular successors to, the first two aortic arches. He described "two pairs of successive vessels," stating that "during the branchial period they serve to supply the substance of the corresponding branchial [pharyngeal] arches" and named them respectively the "earlier" and "later mandibular and hyoid arteries." In the present study a prominent and relatively long hyoid artery was observed constantly until and beyond the time of development of its stapedial branch; but the mandibular artery, with the frequent exception of a small dorsal remnant, dwindles early. Particular attention, therefore, was directed to the question of the blood supply to the mandibular and maxillary regions following the involution of the first aortic arch.

The evidence on which Congdon based his description of "successive channels" consisting of earlier and later mandibular and hyoid arteries is not altogether clear. According to him the "earlier" arteries course near the axis of their corresponding pharyngeal bars and are replaced by the "later" close to the caudal border of each bar; "all break up in a plexus in the subpharyngeal region" and "their current is from the dorsal aorta." Our graphic reconstructions of embryos, including two modeled for Congdon's study, show that the course of each earlier artery is related to the more caudal border of the pharyngeal bar. The terminal part of the long hyoid artery retains this position, but eventually that of the short mandibular artery is swung more cranially. What is more important, the carotid origin of each artery appears to move to the cranial, rather than the caudal, edge of the corresponding bar. In two 4-mm. embryos (no. 836, fig. 39, pl. 4; no. 588, fig. 1), the earlier mandibular and hyoid arteries, identified by Congdon, are relatively large and more or less continuous from dorsal to ventral ends, although branched and somewhat plexiform; here each may be said to supply the substance of its related bar, although not necessarily from the dorsal direction. However, in a 5.7-mm. embryo (no. 1380, reconstructed by Congdon and also for the present study), which is more advanced, only dorsal ends are found, and that of the mandibular artery is reduced to a mere fragment. Certainly the later mandibular artery, which was identified by Congdon in this embryo, does not appear to supply its related bar, since it can be traced for only an insignificant distance laterally from the carotid. Since no evidence was found in the present study for other than retrogression or differentiation, respectively, of the original mandibular or hyoid arteries which succeed the first two aortic arches, the designation "earlier" and "later" will be omitted. The embryos on which the comments above are based will now be described in more detail.

The two 4-mm. embryos (no. 836, figs. 38, 39, pl. 4; no. 588, fig. 1) just mentioned show successive stages in arterial development, the fourth aortic arch being in beginning formation in the first specimen and fully developed in the second. A tortuous plexiform mandibular artery has now replaced the first aortic arch. Its dorsal end dwindles immediately, and its initial course is not only lateral but also caudal, before plexiform connections join it with the lateral and

ventral parts of the same artery in the body of the mandibular bar. This marked caudal deflection in course appears to be dependent upon the oral groove now partly dividing the first pharyngeal bar into definite maxillary and mandibular regions. The most dorsal and lateral parts of the artery are so small and plexiform that its continuity in this region is highly questionable. On the left side of embryo no. 836, the dorsolateral part of this primitive mandibular artery appears to give off small branches which pass over the oral cavity into the emerging maxillary process (fig. 38, pl. 4).

In two more advanced embryos (nos. 1380 and 2841), in which the pulmonary arch is forming, the irregular hyoid artery, which has replaced the second aortic arch of the earlier embryo (no. 588, fig. 1), is definitely interrupted, but the remaining dorsal end is relatively long and extends not only laterally but also ventrally for some distance before dwindling (fig. 2). The mandibular artery is now difficult to identify, there being only a short dorsal remnant.[6] It was not possible to trace any vessels in the mandibular substance of no. 1380; but in no. 2841, which also shows the small dorsal fragment of the mandibular artery almost immediately breaking up into capillaries, there are fairly well defined arteries in the subpharyngeal region. These arise from the aortic sac as irregular bilateral channels in the general position of the ventral ends of the first two aortic arches. Each passes cranially and laterally through the hyoid into the mandibular bar and is lost in a plexus around the mesial border of the mandibular branch of the fifth nerve (fig. 2). Congdon (1922, pl. 2, fig. 35) labeled this the ventral-pharyngeal artery, stating that the vessel originally borders the thyroid primordium, is gradually withdrawn from the mid-line or replaced by a more lateral vessel during the "branchial" period, and finally constitutes a component of the external carotid artery (figs. 30–32, pl. 3).

Other embryos of this period were studied to verify, if possible, the arterial pattern at times equivocally revealed by the four embryos just described. One of 5.5 mm. (no. 3960, cut coronally in 20-micron sections) proved to be a particularly reliable index because all the blood vessels of the head stand out very clearly, engorged with a remarkable natural injection (fig. 3). This embryo belongs to the same age group as no. 2841, and the general arterial configuration is similar, the basilar artery being in early formation in both. A dorsal fragment of each mandibular artery extends laterally from the carotid for a short distance, to be lost in capillaries just cranial and dorsal to the first pharyngeal pouch, as found in the embryos described above. The hyoid artery is definitely larger and much longer than the mandibular artery. It supplies the more dorsolateral part of the hyoid bar and terminates caudoventrally about midway between the ventral limits of the seventh and ninth nerve roots. Of particular significance is the fact that the ventral pharyngeal artery at its origin is large, at least four times the size of the mandibular artery. It divides into ventromesial and dorsolateral branches at the cranial level of the hyoid bar. The more prominent lateral branch, which continues the main stem, extends into the mandibular bar, giving off large branches to its substance before continuing cranially and dorsally over the pharynx to the mandibular nerve root (fig. 3*a*, *c*). This terminal branch is comparable to the "Oberkieferast" of the "external carotid" (ventral pharyngeal artery) described by Fuchs. In this embryo, therefore, it is obvious that the substance of the first pharyngeal bar is supplied not by the mandibular artery, but by the ventral pharyngeal artery, although the second bar continues to be partially supplied by the hyoid artery. This arrangement persists until the end of the "branchial" period, when the stapedial artery is formed.

Meanwhile, the most caudomesial part of the developing maxillary process, in contrast with the craniomesial part supplied by the primitive maxillary artery, may continue to be supplied by the small mandibular artery. This was noted particularly in a 6.8-mm. embryo which is more advanced than the above group (no. 6504, cut sagittally in sections of only 6 microns). Owing to unequal environmental growth, the hyoid artery has assumed a more caudal direction behind the first pharyngeal pouch (see below) and the mandibular artery a more cranial direction over the oral cavity (contrast right and left sides of the younger embryo, shown in fig. 3*b* and *c*). This apparent change in course is also seen in Tandler's models of the rat embryo. The first pouch is now relatively wider than before, and the mandibular

[6] It should be noted that in Congdon's illustration of a model of no. 1380 (his pl. 2, fig. 34), the artery labeled "later mandibular" and shown taking a dorsal course is actually a part of the primitive trigeminal artery to be described in a later section of this paper.

artery has obviously lost all connections of any significance with the lower jaw region. Its domain is the roof of the oral cavity in the area to be traversed by the future superficial petrosal nerve (compare figs. 30 and 31, pl. 3). The question arises whether the artery seen at this stage represents the original mandibular artery or a collateral maxillary branch, as reported in the rat by Tandler (the "infraorbital branch of the dorsal remnant of the first aortic arch"). Since, however, the interruption of the primitive mandibular artery certainly takes place in a position dorsal rather than ventral to the pharynx, and since in no embryo of this series could its remaining dorsal end be followed into the subpharyngeal region, it seems unnecessary to assume more than a slight forward shifting in the direction of the original stem of the artery. Whenever the mandibular artery could be identified at all, following its interruption, it was confined to the region dorsal and cranial to the oral cavity, that is, the developing maxillary process. In some cases during later stages, it constitutes a so-called Vidian artery, although an internal carotid branch accompanying the superficial petrosal nerve is apparently small and inconstant in human development (see below).

It is of interest to compare the next embryo of our series, no. 617, of 7 mm., with that of Tandler's human "stage III," of the same length and practically identical in general arterial development, including the third, fourth, so-called "fifth," and pulmonary aortic arches. The mandibular artery has the same configuration in both embryos. It is shown in a horizontal head section by Tandler in his text figure 27, with its more distal threadlike part labeled "first aortic arch in degeneration [*Rückbildung*]," and also in our figure 31, plate 3. In our horizontal reconstruction, the superficial petrosal (Vidian) nerve is illustrated and was traced to a position just caudal to the mandibular artery, which as yet retains its original caudolateral course. By contrasting figure 31 with the earlier stage shown in figure 30, plate 3, it will be seen that the internal carotid origin of the mandibular artery, as also that of the hyoid artery, appears to have shifted cranially in reference to the delimiting pharyngeal grooves and pouches. As a result, both the mandibular artery (or "maxillary" artery, as it could now be called at the expense of its being confused with the primitive maxillary artery arising from the more distal carotid; see also fig. 13*b, c, d*) and the superficial petrosal nerve which it will soon accompany, in some cases at least, are in position for descent into the roof of the oral cavity during the early "post-branchial" phase (fig. 32, pl. 3).

Both in our embryo and in Tandler's, the distal part of the hyoid artery passes into the caudal confines of the second or hyoid bar. From its more cranial point of origin on the internal carotid, it is now directed caudolaterally as in the corresponding stage in the rat. But it should be noted that the terminal area of the artery remains the same as in the earlier embryos, that is, it courses between the roots of nerves VII and IX, ventral to the tympanic nerve, and is lost near the ninth nerve root and second pharyngeal pouch. These apparent changes in origin, position, and direction of the hyoid artery are explained by the unequal growth in its environment between the 4- and 9-mm. stages. The growing predominance of the mandibular bar, with its advancing maxillary process, over the hyoid and glossopharyngeal bars, the attendant caudal curve of the seventh nerve, and the close grouping of the seventh to tenth nerve roots can best be visualized by a comparison of figure 30 with 31 in plate 3, and figure 2 with 4.

The hyoid artery has not yet given off a branch directed toward the territory of the first aortic arch, but the apparent forward shifting in its carotid origin makes conditions more favorable for such a formation. The ventral pharyngeal artery is conspicuous both in Tandler's embryo (labeled variously "external carotid" and "ventral aorta") and in our no. 617. Furthermore, in our embryo, it was observed to terminate in a plexus around the mandibular nerve root, after skirting the mandibular end of the developing chorda tympani nerve along its mesial border (fig. 31, pl. 3); this approximation of nerve and artery is also seen in the other embryos of this stage, notably no. 163, of 9 mm. (fig. 4*a*).

Tandler's next succeeding stage is a 12.5-mm. embryo which is comparable to our 16- to 18-mm. embryos in general arterial and cerebral development. Here, the stapes primordium and its artery, including all three branches, are well advanced. To determine the formation of these branches, including their main stem, a series of embryos between 9 and 14 mm. were studied and several were graphically reconstructed. Two of 12 mm. (no. 1771, fig. 5; no. 6520) and two

of 14 mm. (no. 940, fig. 6; no. 6258), which are all definitely younger than Tandler's 12.5-mm. embryo, show a large cranially directed offshoot from the hyoid artery. This collateral immediately passes through the condensation of mesenchyme representing the stapes and therefore constitutes the definitive stem of the stapedial artery. It lies dorsal to the first pharyngeal pouch just under the marked caudal curve in the course of the seventh nerve, and is in the same position as the anastomotic branch between the dorsal remnants of the first and second aortic arches, which appears in both rat and rabbit embryos. In one of the 14-mm. embryos just mentioned, it was possible to trace a definite anastomosis between the new stapedial collateral and what is undoubtedly the distal remnant of the ventral pharyngeal artery. This specimen (no. 6258, not available for reconstruction) is cut horizontally in 10-micron sections and the smaller arteries are marked by a good natural injection. Since it so closely resembles in body form and in general arterial and nervous development our reconstructed embryo of 14 mm. (no. 940), the distal connections of the stapedial artery in the former embryo could easily be superimposed freehand on the basic reconstruction of the latter (fig. 6; fig. 32, pl. 3). In this significant early stage of the postbranchial phase, the stem of the hyoid artery no longer appears to be within the hyoid bar, owing to the environmental shifting and unequal growth foreshadowed in the preceding stage. Rather, the origin of the hyoid artery from the internal carotid appears to be actually in front of the first pharyngeal pouch and cleft as shown in both horizontal (fig. 32, pl. 3) and bilateral (fig. 6) views of embryo no. 940. The collateral branch of the hyoid artery, which is now the stem of the stapedial artery, is therefore in an entirely favorable position for anastomosis with vessels in the lateral mandibular substance. In all the embryos of this stage, the distal end of the hyoid artery, so prominent in earlier stages, is reduced to a small remnant which passes almost directly caudally along the tympanic branch of the ninth nerve, an association observed with regularity in both younger and older embryos. This hyoid remnant, including its large proximal part now serving as the stem of the stapedial artery—in other words, the whole length of the original hyoid artery—is retained as the small caroticotympanic branch of the adult internal carotid. The ultimate dwindling or interruption of the stapedial artery during embryonic life occurs not at the carotid artery, but at the stapes, that is, at the most proximal end of the stapedial collateral given off by the hyoid artery (figs. 33–36, pl. 3). Therefore, the adult caroticotympanic artery represents, strictly speaking, not a remnant of the stapedial, as noted by various anatomists, but the whole embryonic hyoid artery.

The definitive stem of the stapedial artery, whose formation has just been described, gives off immediately beyond the stapes a cranial offshoot (the future supraorbital division) which can be traced a short distance lateral to the Gasserian ganglion. The continuation of the main artery (as seen in a 14-mm. embryo, no. 6258), which represents the lower or maxillomandibular division of the stapedial, courses ventrally along the mandibular nerve to join a plexiform vessel at the root of the chorda tympani nerve. This vessel may be followed caudally along the chorda tympani for about one-half its distance (i.e. the mandibular as contrasted with the hyoid part of the nerve); here it turns somewhat mesially in the direction of the component of the external carotid artery, where it dwindles and is lost (fig. 32, pl. 3). The primitive external carotid, representing the proximal end of the ventral pharyngeal artery (Congdon, 1922), now originates from the third aortic arch, which is about to lose its identity in becoming the definitive common carotid artery. The subpharyngeal vessel, with which the stem of the stapedial has made the anastomosis just described, undoubtedly represents the distal end of the earlier ventral pharyngeal artery, which, it will be recalled, extended to and accompanied the mandibular end of the chorda tympani nerve (fig. 31, pl. 3). The present interruption of the ventral pharyngeal artery has occurred as a result of the disintegration of the aortic arch system and the new suprapharyngeal connections now established by the stapedial artery between the realms of the first and second aortic arches. In summary, the stapedial artery forms as a collateral of the hyoid artery and annexes the distal end of the ventral pharyngeal artery to form the stem of its maxillomandibular division. This anastomosis occurs at the mandibular root of the fifth nerve, so that the mandibular is the first of the three definitive branches of the stapedial to be formed. The maxillary branch is a secondary derivative of the mandibular branch, and the supraorbital

division is a derivative of the main stem of the stapedial artery. The point of origin of these three stapedial branches from their common stem, it will be noted, is not the same as the configuration in the rabbit, which in turn is unlike that in the rat (see p. 231 above).

The fate of the primitive mandibular artery was indicated during the early postbranchial stages of this series. As shown above, the small remnant of this artery, arising from the internal carotid, lies in the path of the developing superficial petrosal nerve during the branchial period (fig. 31, pl. 3). Later, when the nerve has reached and passed closely by the lateral aspect of the internal carotid, the mandibular artery may sometimes be seen to accompany the nerve for a short distance. In one embryo (no. 544, 11.5 mm., an injected specimen) this artery was prominent enough on the right side to be followed cranioventrally for some distance into the well developed maxillary process (fig. 40, pl. 4). It could not be definitely determined whether it communicated with the laterally placed maxillary branch of the stapedial artery, then in formation, because of the rich venous plexus in this region; however, in an 18-mm. embryo (no. 1390) one could trace a questionable plexiform communication (fig. 7*a*). Failure to find a so-called Vidian artery in other embryos does not prove its nonexistence, but one can be certain that it does not at any stage in man attain the importance found in many adult reptiles or in the bat embryo, mentioned above. Several textbooks of anatomy describe an adult Vidian artery (or artery of the pterygoid canal) as a small inconstant branch of the internal carotid, arising within the petrosal bone just above the small caroticotympanic branch which represents the embryonic hyoid (stapedial) artery. This Vidian artery is sometimes said to anastomose with a branch of the descending palatine artery (from the internal maxillary). But more commonly, according to most anatomists, the artery in the Vidian canal is a branch of the distal (originally stapedial) part of the internal maxillary artery. The present observations on the history of the mandibular artery may be summarized as follows: Following the involution of the first aortic arch, the dorsal end of the succeeding mandibular artery is interrupted at the craniodorsal margin of the first pharyngeal pouch, and its abbreviated dorsal remnant, therefore, remains entirely suprapharyngeal, limiting its domain to the maxillary region; it sometimes constitutes a small Vidian artery after the superficial petrosal nerve develops as far as the contiguous part of the artery at its origin from the carotid; it does not enter into the formation of any branches of the stapedial artery, as is the case in the rat, and is ultimately taken over in many cases by the internal maxillary artery. Both the Vidian (embryonic mandibular) and the caroticotympanic (embryonic hyoid and stapedial) arteries are significant in the adult as potential sources of collateral circulation between the internal and external carotid arteries.

THE OPHTHALMIC ARTERY

At the time when the maxillomandibular division of the stapedial artery is formed, as discussed in the foregoing account, one finds only the stem of origin for the future supraorbital division. This arises just beyond the stapes from the common stem supplying the bulk of the upper and lower jaws, and is first traced to the region of the eye in embryos of approximately 18 mm. Its history cannot be comprehensively discussed without a consideration of the development of the ophthalmic artery, since man, like many lower forms, shows a close association between these respective components of the adult external and internal carotid systems.

No description of early stages in the development of the eye vessels in man has appeared. Versari, in a series of papers appearing from 1900 to 1923 (references given in Mann, 1928), and Dedekind (1908–1909) dealt with older stages, beginning with embryos of approximately 20 mm. Mann, in a 1928 monograph on the development of the human eye, recapitulates the work up to that time and devotes considerable attention to fundamentals of optic vascularization, although unfortunately it is difficult to orient oneself in reference to the description and illustrations of her younger embryos. These authors were chiefly concerned with the complicated details of development and retrogression in the strictly ocular blood system, and do not give any clear idea of the related stages in the formation of the whole ophthalmic artery, including orbital as well as optic branches. Since the present study shows that the permanent adult stem of the ophthalmic artery does not appear

until the 18-mm. stage and many of its branches are not recognizable until later, it is important to know, in reference to all earlier specimens, from what part of what parent stem any "ophthalmic artery" under discussion arises and what are the environmental relations. The detailed study of the eye vessels in the rabbit by Fuchs (1905) appears to be the only complete account of the subject, though he also was not always specific as to the larger related arteries in successive stages. His work reveals that all the arteries to the region of the eye, orbital and ocular, have a relatively complex history which the present study showed to be equally involved in man.

ler (1902) gives several figures of a young rat embryo (his stage II) wherein the arteries cranial to the first aortic arch are named in a misleading if not erroneous manner. His illustrated model "stage II" (his pl. 3, fig. 4) shows the "cerebral carotid" (primitive internal carotid) dividing into two branches of equal size. The "anterior ramus," passing ventrally just in front of the oral cavity, gives off the ophthalmic artery (his text fig. 6). The "posterior ramus" extends

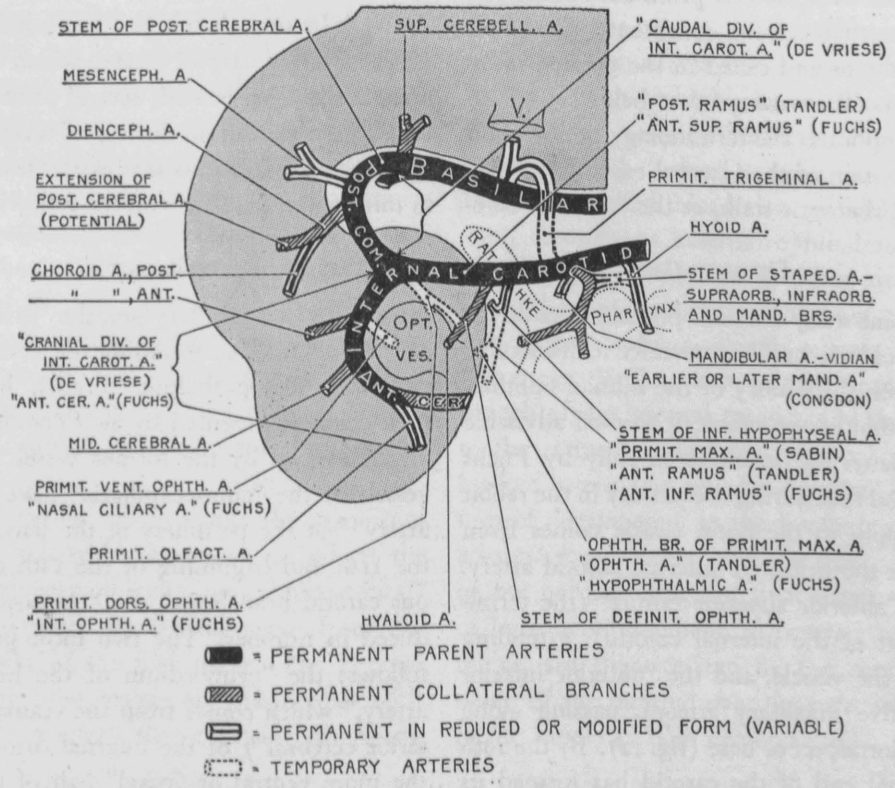
STEM OF POST. CEREBRAL A.
SUP. CEREBELL. A.
"CAUDAL DIV. OF INT. CAROT. A." (DE VRIESE)
MESENCEPH. A.
V.
"POST. RAMUS" (TANDLER)
"ANT. SUP. RAMUS" (FUCHS)
DIENCEPH. A.
BASILAR
EXTENSION OF POST. CEREBRAL A. (POTENTIAL)
PRIMIT. TRIGEMINAL A.
POST. COM.
HYOID A.
CHOROID A., POST.
" " , ANT.
INTERNAL CAROTID
STEM OF STAPED. A.- SUPRAORB., INFRAORB. AND MAND. BRS.
OPT. VES.
PHARYNX
"CRANIAL DIV. OF INT. CAROT. A." (DE VRIESE) "ANT. CER. A." (FUCHS)
MANDIBULAR A.-VIDIAN "EARLIER OR LATER MAND. A" (CONGDON)
ANT. CER.
STEM OF INF. HYPOPHYSEAL A. "PRIMIT. MAX. A." (SABIN) "ANT. RAMUS" (TANDLER) "ANT. INF. RAMUS" (FUCHS)
MID. CEREBRAL A.
PRIMIT. VENT. OPHTH. A. "NASAL CILIARY A." (FUCHS)
OPHTH. BR. OF PRIMIT. MAX. A. "OPHTH. A." (TANDLER) "HYPOPHTHALMIC A." (FUCHS)
PRIMIT. OLFACT. A.
PRIMIT. DORS. OPHTH. A. "INT. OPHTH. A." (FUCHS)
HYALOID A.
STEM OF DEFINIT. OPHTH. A.
= PERMANENT PARENT ARTERIES
= PERMANENT COLLATERAL BRANCHES
= PERMANENT IN REDUCED OR MODIFIED FORM (VARIABLE)
= TEMPORARY ARTERIES

FIG. 12. Composite diagram of the arteries around the embryonic forebrain to illustrate differences in terminology employed by various writers. Their names are in parentheses, their designations are in quotation marks, and those adopted or orginated for this study are underlined. This variation in terminology must be noted in reference to any correlation of the development of the human stapedial and ophthalmic arteries with that described for other species.

A discussion of the earliest arterial supply to the region of the eye cannot be pursued without some clarification of terminology, since the literature shows a considerable diversity in both the naming and the interpretation of the many vessels of this territory. These differences together with the terms adopted in the present discussion have been illustrated in diagrammatic form in figure 12. For instance, Tandcranially toward the brain. It is clear (see the transverse sections of the same embryo in his text figs. 4, 5) that the anterior ramus, just mentioned, in passing caudal to the optic vesicle cannot be in the position of the terminal cerebral part of the primitive internal carotid, which he also designated as the "anterior ramus" in his later stages (his text fig. 9). Again, "posterior ramus" as designated in the successive stages of his text figures 6, 9, and plate 3 has two meanings: in one sense it is used for the primitive internal carotid extending to the forebrain, and in the other it refers to the later caudal division of the

internal carotid (posterior communicating artery). Fuchs (1905) points out that Tandler's "anterior ramus" is identical with an artery which gives off a temporary "hypophthalmic" branch in the very young rabbit embryo, and which he calls the "anterior inferior ramus" in contradistinction to the terminal cerebral part of the carotid, named the "anterior superior ramus." The anterior and the anterior inferior rami of these writers not only are the same artery, but are clearly comparable with the first prominent branch of the primitive internal carotid consistently found in early human embryos and called in the present study the "primitive maxillary artery" (see below).

Fuchs also complicates the terminology by referring to the cranial division of the internal carotid, curving cranially around the optic stalk, as the "anterior cerebral artery," and does not always identify various collateral branches of this artery, although several are illustrated in certain figures. As fully clarified by De Vriese (1905), what Fuchs and others called the "anterior cerebral" is the primary cranial, as contrasted with the primary caudal, division of the primitive internal carotid. Only in later stages when the cranial division gives off the middle cerebral collateral branch, which defines the full cerebral extent of the adult internal carotid, does the anterior cerebral stem of origin become definitive. The whole terminal part of the internal carotid artery, which lies against the brain wall, together with several primitive derivatives (fig. 12), is concerned during its inception with optic supply, and its various landmarks must be kept well in mind in connection with the following descriptions.

Development of the Ophthalmic Artery in the Rabbit

Since the present study does not pretend to cover all details of the subject, but has revealed considerable similarity between the history of the human ophthalmic artery and that of the rabbit, it seemed advisable to outline the latter as described so fully by Fuchs (1905). He found that during the 9th day in the rabbit embryo the supply to the optic vesicle comes from two branches of the primitive internal carotid artery. These are the "anterior superior ramus" (the terminal cerebral part of the internal carotid), extending craniodorsal to the vesicle, and the "anterior inferior ramus" (primitive maxillary artery), passing along its ventroposterior aspect or base (fig. 12). By the 10th day, the terminal end of the carotid has formed its cranial ("anterior cerebral") and caudal ("posterior communicating") divisions and the former supplies the most cranial aspect of the vesicle. The internal carotid, opposite its caudal division, gives off the "primordium of the permanent internal ophthalmic artery." It should be noted that the stem of the "internal ophthalmic" in the rabbit is comparable (in reference to its destination, though not its origin) to that of the ophthalmic artery of man and is so named in contradistinction to the "external ophthalmic artery" of the rabbit, which is developed later from the external carotid. In addition to the sources of optic supply just mentioned, there is also a branch from the anterior inferior ramus of the carotid (primitive maxillary artery); this is a highly transitory "hypophthalmic artery" (fig. 12). All these arteries soon lose themselves in a capillary net, the "primordium of the choriocapillaris," surrounding the vesicle. At the 11th day, the "hypophthalmic" branch has disappeared, now being represented by an elaborate plexus in the area traversed by the former vessel. The plexiform vessels of the "choriocapillaris" have met in a "ring artery" [7] at the periphery of the lens. At the end of the 11th and beginning of the 12th day, the numerous carotid branches to the "choriocapillaris" are reduced in number. The two most prominent are as follows: the "primordium of the long nasal ciliary artery," which comes from the cranial division ("anterior cerebral") of the internal carotid and supplies the more ventral or "nasal" half of the eye, and the previously established stem of the internal ophthalmic artery, which now has a "long temporal ciliary branch" supplying the more "temporal" or dorsal half of the eye; these arteries lose themselves in the choriocapillaris. From the caudal side of the "ring artery," a "blind bud" arises to pass mesially between the optic cup and lens into the outer part of the fetal ocular cleft [8] (choroid fissure); this is the "primordium of

[7] Mann (1928) notes that Versari called the counterpart of this vessel a vein in the human embryo and that, in view of the "peculiarities of both fetal and adult ocular circulation," it is better to call it simply the "annular vessel."

[8] Mann argues against the use of the term "choroid fissure," since it "tends to create the impression that the cleft has some connection with the choroid." Furthermore, the origin of one of the primitive ophthalmic arteries of the human embryo bears a definite relation to the anterior choroidal artery, which supplies the cerebral choroid plexus. The term she suggests, "fetal ocular cleft," will be used here.

the primary hyaloid artery." At the end of the 12th day, the internal ophthalmic artery has two divisions, the stem of the long temporal ciliary branch and the "primordium of the definitive stem of the hyaloid artery." The primary hyaloid artery, which was previously formed, has become dilated into the "bulbus arteriosus hyaloideus," which is now connected with the ring artery by four branches, two dorsal and two ventral. The mesial end of the "bulbus" soon develops a secondary anastomosis with the choriocapillaris through the medial aspect of the fetal ocular cleft. By the 13th day, the internal ophthalmic is the largest optic branch of the internal carotid, and its derivative, the definitive stem of the hyaloid artery, has anastomosed with the "primordium of the primary hyaloid artery" lying within the fetal ocular cleft, thereby completing the definitive hyaloid artery. The bulbus is then resolved into the branches of the vascular tunic of the lens. The remaining branch to the eye is a prominent long nasal ciliary artery whose origin, exactly as in the earlier stages, is from the most cranial curvature of the cranial division of the internal carotid (Fuchs' "anterior cerebral artery").

The 14th day in the rabbit marks the significant second phase of related development, in which the stapedial artery has formed, including a "bulbo-orbital" branch associated with the frontal nerve from the ophthalmic division of the fifth nerve. The internal ophthalmic artery now makes an anastomosis with the long nasal ciliary artery, thus annexing this primitive branch of the most distal end of the internal carotid. Fuchs emphasizes that at this stage the internal ophthalmic artery, including bilateral long ciliary and hyaloid branches, constitutes the sole supply to the eye, while the stapedial artery, through its orbital branch, alone supplies the orbit. From the 15th day, there take place the final changes which characterize the optic and orbital arteries in many vertebrates. In the rabbit these are, in brief, the annexation by the external carotid of practically all the arteries to the region of the eye. The branches of the stapedial artery are first taken over by the external carotid as in the human embryo. Later, the orbital branch of the external carotid (formerly stapedial) not only develops all the orbital arteries (such as branches to the lacrimal and Harderian glands), but also takes over, through its external ophthalmic division, both the long nasal and temporal ciliary arteries, previously established as branches of the internal ophthalmic artery. Except for a variable anastomotic connection, this annexation leaves to the small internal ophthalmic branch of the internal carotid only the role of supply to the retina through the proximal remnant of the hyaloid artery. As will be described below, the pattern of development in the human embryo up to the 20-mm. stage closely parallels that of the rabbit up to, but not including, the final stages. The last stages of human development, in contrast with that of the rabbit, are characterized by the complete predominance of the internal over the external carotid artery in the supply to both eye and orbit.

The Primitive Ophthalmic Arteries in Man

In the 1912 review by Evans it is noted, in statements based on earlier reports, that the ophthalmic artery is the first branch of the internal carotid to develop and that in embryos of 7 mm. it divides into bilateral long ciliary and hyaloid branches. This is illustrative of Sabin's (1917) warning against a premature naming of embryonic vessels. The ophthalmic arteries of this stage are only part of an elaborate plexus, components of which will later give rise to but a small part of the adult ophthalmic artery. However, a large primitive branch, which is temporarily directed toward and gives off tributaries to the base of the optic vesicle, does represent the first cerebral branch of the internal carotid artery. This ventrally directed branch was first seen in embryos of 3 to 4 mm. and was noted by Tandler (see above) and Sabin in reference to rat and pig embryos respectively. Fuchs showed that supply to the optic vesicle by this artery, through a temporary "hypophthalmic" branch, is exceedingly transitory in the rabbit, and the present study shows this finding to be equally true for the human embryo. Since the stem of the vessel persists in relatively reduced form to supply the most mesial parts of the maxillary region around Rathke's pouch, Sabin's term "primitive maxillary artery" (1917, not discussed by her but so designated in the labeling of a 6.5-mm. pig), is used in the present account.

Although supply to the optic region by this primitive maxillary artery is lost at an early stage, its sub-

sequent history is a matter of interest. The artery is prominent in all the earliest embryos of this series and, although not named, is either described or illustrated in connection with those of Ingalls (1907), Elze (1907), and Davis (1923). Like the mandibular artery described above, this vessel is mesial rather than lateral and takes no part in the formation of the maxillomandibular division of the stapedial artery. Its origin is well ahead of the first aortic arch, from the most mesial curve of the internal carotid, and its course is primarily ventral through the tissue bordering the neck of Rathke's pouch. In two embryos of 4 mm. (no. 836, fig. 38, pl. 4; no. 588, fig. 1 and fig. 44, pl. 5) the artery vascularizes the base of the undifferentiated optic vesicle and the neighboring caudomesial tip of the prosencephalon. In two older embryos of between 5 and 6 mm. (nos. 1380 and 3960), wherein the optic cup and stalk are in beginning formation, the artery is still relatively large and conspicuous, with its primary termination at the prosencephalon. It gives off both a mesially directed branch, passing between the base of Rathke's pouch and the brain wall (fig. 3*a*), and a lateral branch to the developing cleft in the optic vesicle (left side of embryo, fig. 3*b*) which is most suggestive of the transitory "hypophthalmic artery" seen in the 10-day rabbit embryo (fig. 12). After the 5- or 6-mm. stage, when its primitive role of supply to the cerebral and optic regions is transferred to branches of the more cranial part of the internal carotid, the primitive maxillary artery dwindles in size (fig. 2). Between the 6- and 12-mm. stages it was not always identified on both sides and, when seen, could usually be traced for only a short distance ventrally from the carotid. As seen in the lateral views of successive stages up to 14 mm., the artery is consistently at the level of the maxillary branch of the fifth nerve and maintains its original position just lateral to the base of Rathke's pouch.

In an 18-mm. embryo (no. 1390, fig. 7), in which the neck of the hypophyseal diverticulum has become much attenuated, there is a small branch of the internal carotid (two branches on one side) in the position of the primitive maxillary artery. These now pass more mesially than ventrally toward the small craniopharyngeal canal, to which the wide neck of Rathke's pouch is now reduced, and border the caudal part of the hypophyseal diverticulum (two branches were seen on one side in one earlier embryo, no. 2841 of 5.3 mm.). In a 24-mm. embryo (no. 632, injected by Evans) the lumen of the craniopharyngeal canal is obliterated, and the anterior hypophysis is fairly well differentiated and partly surrounds the infundibular process. The internal carotid, proximal to the ophthalmic artery, gives off two bilaterally symmetrical branches which could be followed mesially only as far as the hypophyseal border, although they undoubtedly enter this structure (fig. 8*a;* fig. 35, pl. 3). The most cranial branch, arising just below the definitive stem of the ophthalmic artery, apparently anastomoses with the caudal branch skirting the caudal margin of the hypophysis,[9] after giving off a branch passing between the gland and the brain. One or both of these carotid branches must represent the primitive maxillary artery, which now appears to be concerned with vascularization of the hypophysis.

As is now known, the blood supply of the adult hypophysis, which includes a portal system, is very complex, and the material of this paper adds no significant developmental details. Several points of general interest, however, should be noted. In the first place, it is clear that the primitive maxillary artery, in spite of its early association with Rathke's pouch, does not become an artery of supply to the anterior hypophysis, which is derived from this pouch. The emergence of the permanent stem of the ophthalmic artery during the 18-mm. stage, in a position cranial to the primitive maxillary artery, tends to confine the origin of the latter to the intracavernous part of the internal carotid. It has been shown that the anterior and posterior hypophyseal lobes, in a series of mammals including the rhesus monkey and man (Wislocki and King, 1936), have independent arterial supplies derived from two separate sources. That to the anterior hypophysis (pars distalis) and pars tuberalis arises from numerous minute "pial" branches from the intracranial internal carotid (that is, above the stem of the ophthalmic artery) and the posterior communicating arteries. The less highly vascularized infundibular process is supplied by one or two bilateral "dural" branches of the intracavernous carotid, that is, the carotid segment which gave origin to the primitive maxillary artery. The "superior hypophyseal arteries" (Wislocki, 1937) to the anterior hypophysis in

[9] It should be remembered that the caudal or posterior border of the hypophysis in the embryo head, which is bent forward over the chest, represents the ventral or inferior border in the adult.

the human embryo were first identified in the present series in an injected embryo of 11.5 mm. (fig. 40, pl. 4). They are represented at this stage by numerous plexiform branches from the carotid and posterior communicating arteries; these branches spread mesiocaudally over the diencephalic floor and surround the more cranial borders of Rathke's pouch. In this embryo the neck of the diverticulum is still wide open, the infundibulum is undeveloped, and the primitive maxillary artery, as in other embryos of this stage, is only a short carotid twig. As noted above, no derivative of the primitive maxillary artery was definitely traced to the developing hypophysis until the 20- to 24-mm. stage (fig. 35, pl. 3), and the vessels seen at this time must undoubtedly represent the inferior hypophyseal arteries. This finding is in line with Wislocki's statement that the "infundibular process does not receive its definitive vessels until it attaches to the dura" and thus is "vascularized at a relatively late period and very slowly."

A further detail reported in the adult dog by Dandy and Goetsch (1911) is of interest in connection with the fate of the primitive maxillary artery. Here the supply to a small epithelial body lying at the base of the gland in the floor of the sella, namely, the "parahypophysis which is evidently a remnant of Rathke's pouch," comes bilaterally from two small arteries of cavernous carotid derivation. The more cranial branch passes directly mesially from the carotid to the parahypophysis. The caudal one also sends a branch to the parahypophysis before joining its fellow of the opposite side to form the sole artery of the posterior hypophysis. Certainly one, and perhaps both, of these arteries must represent the primitive maxillary artery which is first seen in 3- to 4-mm. human embryos as a prominent carotid branch, bordering the lateral margins of the hypophyseal diverticulum. After the early and complete loss of its primary role of supply to the prosencephalon and base of the optic vesicle, the stem of the primitive maxillary artery is retained to become incorporated ultimately in the formation of the inferior hypophyseal arteries.

The configuration of all the primitive arteries to the developing human eye during various stages will now be described. In the youngest embryo of this series (no. 2053, 20 somites) the primitive carotid terminates in a plexus at the caudal aspect of the emerging optic vesicle (fig. 37, pl. 4). In a 4-mm. embryo (no. 836) the internal carotid extends farther cranially to surmount the dorsal aspect of the optic vesicle, giving off en route the well defined primitive maxillary artery (described above), which proceeds ventrally to the base of the prosencephalon (fig. 38, pl. 4). In another 4-mm. embryo (no. 588, fig. 1) the terminal cerebral part of the carotid has branched into its cranial and caudal divisions. In place of the diffuse plexiform supply of the earlier stages, there are several more definite branches to the optic vesicle; the most notable one, which has been named for this account the "primitive dorsal ophthalmic" artery, leaves the carotid at its point of division. In a comparable embryo, that of Ingalls (1907, pictured by Evans, 1912, fig. 417), this was prematurely labeled the "ophthalmic artery."

During the 4- to 6-mm. stages, the optic vesicle differentiates into the short optic stalk and the optic cup, with a wide-mouthed indentation which is beginning to enclose the lens primordium. Beginning with this period, six stages in the development of the ophthalmic arteries are illustrated in semidiagrammatic form in figure 13. As is shown in detail in figure 3*b*, the two sides of the embryo (no. 3960) on which the composite figure 13*a* is based show two successive stages in arterial development around the eye. On the left side the optic stalk is short and, owing partly to an asymmetrical rotation of the forebrain, is close to the origin of the primitive maxillary artery, which still gives a branch to the ventrocaudal aspect of the cup where the fetal ocular cleft is forming. But on the right side, all direct connection between this artery and the eye has been lost. On this side there has formed a large, more distal branch of the internal carotid, arising at the point of its cranial and caudal division. This artery immediately subdivides; its shorter branch, passing to the mesial face of the optic vesicle, is the primitive dorsal ophthalmic artery first seen in less advanced embryos (figs. 1, 2); the recent and more prominent derivative is an artery which pursues a long lateral course to pass over the caudodorsal rim of the optic cup. This somewhat plexiform vessel encircles the caudoventral aspect of the ectodermal lens pit and then dips into the depression which represents the fetal ocular cleft. It is obviously the counterpart of the primitive internal ophthalmic artery which supplies the ring artery of the lens in the 11-day rabbit embryo (see figs. 191–194 of Fuchs,

1905). Mann (1928, figs. 31, 158) pictures a model of a 5-mm. human embryo which is comparable to our 5.5-mm. embryo (fig. 3). Although it is difficult to orient oneself as to the surrounding structures in her illustrations, it is highly probable that the vessels shown, one of which, "the future hyaloid artery," is "penetrating the interior of the cup, the other vascularizing its margin," belong to the prominent dorsal ophthalmic branch of the carotid just described. Although the artery does appear to come from "below" in her illustrations because of the angle at which the model of the eye is viewed, the carotid origin of the vessel would be dorsal to the eye in reference to the whole embryo head. It should be borne in mind that the primitive dorsal ophthalmic artery is actually caudodorsal in relation to the cup and stalk, just as an opposing primitive artery, to be described presently, is cranioventral in this relation. Like the 11-day rabbit embryo, this specimen shows several other irregular branches from the cranial division of the internal carotid artery as it curves cranial to the stalk; these supply the more cranial and ventral regions of the optic vesicle.

The next available stage is represented by embryo no. 163 of 9 mm. (fig. 4*a*), which has a good natural injection of vessels in the region of the eye. Here the primitive dorsal ophthalmic artery, which arises in the position of the permanent internal ophthalmic artery of the rabbit and was seen in the preceding human stage, is again large and conspicuous. However, after coursing directly laterally it now appears to end abruptly in a manifold plexus over the dorsal aspect of the optic cup, and no definite single branch can be traced into the cup or fetal ocular cleft as formerly. The plexus covering the optic cup is connected, however, with a more or less complete annular vessel which surrounds the periphery of the lens at the outer margin of the cup; this vessel in turn communicates with a sinus-like blood vessel within the fetal ocular cleft (fig. 13*b*). The latter vessel (a primitive hyaloid artery) also communicates through plexiform channels with the more mesial part of the optic capillary mesh and drains into the multiform veins in the maxillary process. Detailed stages, analogous to the complex development of the hyaloid artery described in the rabbit, were not determined for the present study, but sections of no. 163 (9 mm.) [10] are similar in microscopic appearance to those of the 12-day rabbit embryos illustrated by Fuchs (his

[10] For this embryo there exist only tracings without orientation guide lines, and, since the optic vascularization was seen to be highly plexiform, no attempt was made to reconstruct it in detail.

FIG. 13. Six stages in the development of the ophthalmic artery and the related supraorbital division of the stapedial artery. (Ventral views showing the right side of the embryo.)

a. Approximately 4 to 5 mm. The primitive maxillary artery sends a temporary branch to the base of the optic vesicle, but the primordial cup and lens are supplied by a large primitive dorsal ophthalmic artery.

b. Approximately 9 mm. The primitive dorsal ophthalmic artery now terminates in a plexus investing the optic cup, which is also supplied by a new ventral ophthalmic artery. An annular vessel surrounds the lens at the margin of the cup and connects with an irregular primitive hyaloid vessel within the fetal ocular cleft. Note the relative position of the hyoid and ventral pharyngeal arteries in comparison with those of the preceding figure.

c. Approximately 14 mm. Both dorsal and ventral ophthalmic arteries are elongated and the dorsal one has developed a direct branch to the lens, the definitive hyaloid artery. A collateral (stapedial) branch of the hyoid artery has captured the distal end of the ventral pharyngeal artery, the proximal end of which is now represented by the stem of the external carotid.

d. Approximately 18 mm. The elongated stem of the primitive dorsal ophthalmic artery has been replaced by a more direct vessel, the permanent stem of the ophthalmic artery. A secondary anastomosis joins its hyaloid branch to the primitive ventral ophthalmic artery, which is subsequently interrupted mesially beneath the cartilage primordium of the orbital roof. The stapedial artery has formed its two primary divisions, and the supraorbital one passes into the orbital cavity and borders the ophthalmic nerve.

e. Approximately 20 mm. The supraorbital division of the stapedial artery, the stem of which is dwindling, has developed several orbital branches and is being annexed by the ophthalmic artery, whose ocular branches were established in the preceding stage. Note the arterial ring by means of which the ophthalmic artery passes around to the dorsal side of the optic nerve. Following a similar formation, the internal maxillary artery reaches the outer side of the mandibular nerve root.

f. Approximately 40 mm. The conformation of the ophthalmic artery is recognizably adult following the interruption of two vessels, namely, the cranioventral segment of the arterial ring around the optic nerve; and the supraorbital division of the stapedial artery, whose orbital part has been augmented to form the lacrimal artery. The remainder of the supraorbital division is incorporated in the anterior branch of the middle meningeal artery.

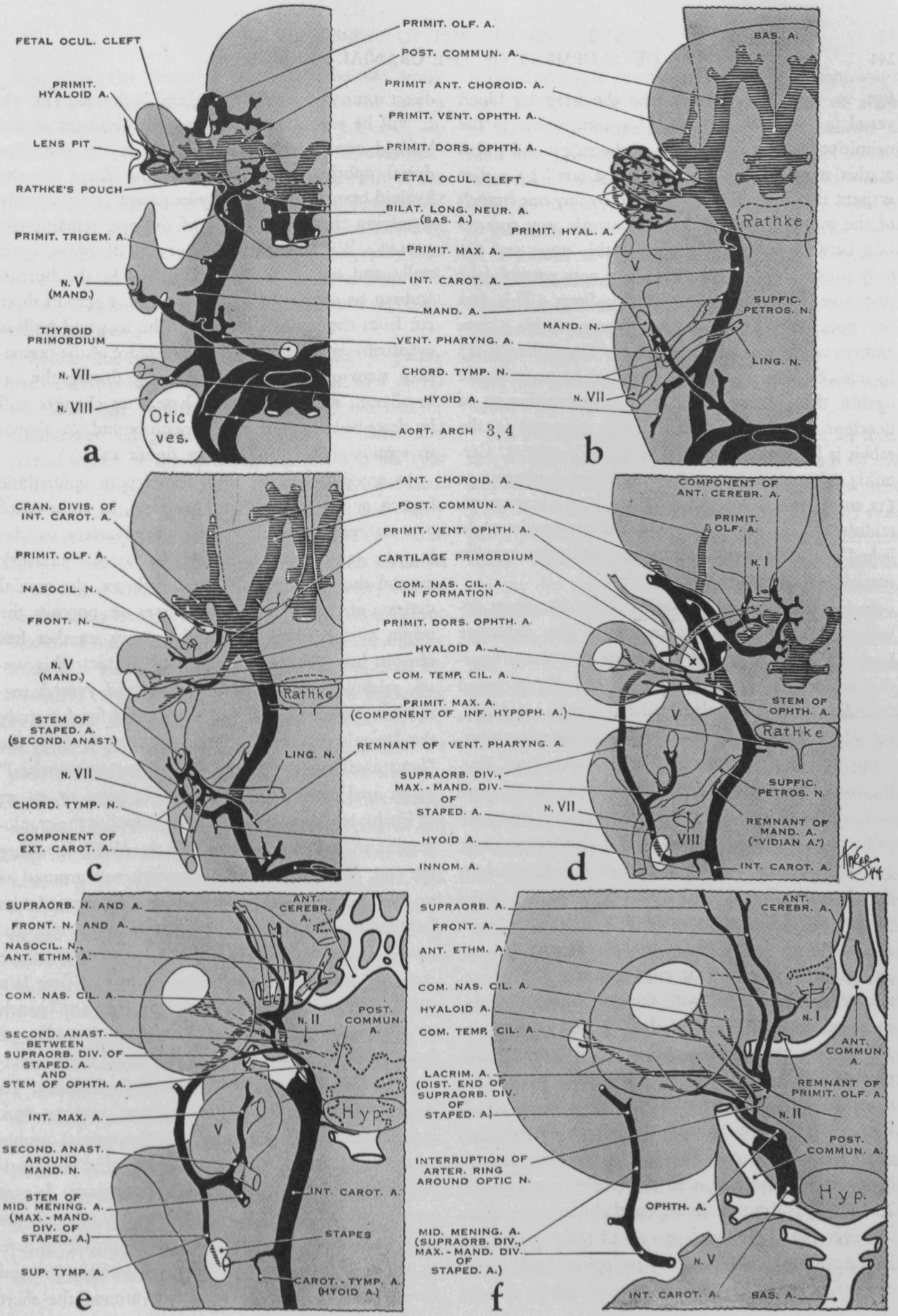

FIG. 13 (legend on page 242)

figs. 20, 21). It is obvious that the irregular blood vessel in the fetal cleft, probably comparable to the primitive "bulbus hyaloideus" of the rabbit and called at this stage in man the "hyaloid artery" by earlier writers, is not yet directly supplied by any one branch of the internal carotid. In other words, any connection between a hyaloid artery of this stage and the only conspicuous ophthalmic artery now present (the primitive dorsal artery) is very indirect. This fact was noted by Elze (1907) in reference to his 7-mm. embryo and discussed more fully by Barniville (1914) in one of 8.5 mm. There appears to be no evidence against the assumption that the complex process of development of the hyaloid artery reported in the rabbit is largely repeated in the human embryo. Certainly it is not until well along in the succeeding stage (11 to 14 mm.) that the primitive hyaloid artery establishes direct connection with the previously established primitive dorsal ophthalmic artery through the mesial end of the fetal ocular cleft.

In looking for an explanation of the circuitous development and late appearance of the definitive hyaloid artery, one must remember that the primordial ectodermal lens, which is relatively far removed laterally from the only available source of blood, namely, the internal carotid, gradually becomes overhung by the developing rim of the optic cup. Furthermore, the fetal ocular cleft developing in the more ventral part of the optic vesicle soon becomes diametrically opposed, in reference to the developing stalk and bulb, to the nearest source of blood, which is the dorsally placed internal carotid near its cranial and carotid divisions (compare figs. 2 to 6). As soon as the capillary mesh (primitive choriocapillaris) begins to envelop the optic cup (according to Mann, this occurs "pari passû with the development of pigment in the outer layer of the cup" between the 7- and 10-mm. stages), this plexus also is interposed in the path of the previously established primary ophthalmic artery (primitive dorsal ophthalmic), which formerly extended without plexiform interruption from the internal carotid artery to the lens. It is to be expected, therefore, that the detour made to the lens by the primitive dorsal ophthalmic artery, passing over the caudodorsal margin of the cup into the lateral (outer) end of the developing fetal ocular cleft (fig. 3), will eventually be replaced by a more direct route through the mesial end of the cleft (fig. 5). It will be seen that, even after establishment of the hyaloid artery as a direct branch of the primitive dorsal ophthalmic artery, the route taken by the hyaloid branch, as well as by its parent artery already supplying the dorsal aspect of the eye, remains circuitous. With further development of brain, optic stalk, and eye, it becomes more so. In the human embryo, as contrasted with the rabbit, a second short cut from the internal carotid to the lens and bulb is eventually established by the appearance of the permanent stem of the ophthalmic artery during the 14- to 18-mm. stages (fig. 7). These later changes will be described in more detail presently and are shown in semidiagrammatic form in figure 13.

As noted above, the most conspicuous ophthalmic branch of the internal carotid artery, in embryos of 7 to 12 mm., is the primitive dorsal artery supplying the caudodorsal parts of the vascular network around the optic cup. In these embryos, the cranial division of the internal carotid gives off, opposite the origin of the anterior choroidal artery, another less obvious but definite optic branch (fig. 4*a*); this vessel, arising from the most cranial and ventral segment of the internal carotid, was named for this study the "primitive ventral ophthalmic" artery. Like the "long nasal ciliary" branch of the "anterior cerebral" in an analogous stage of the rabbit (figs. 17, 19, 23 of Fuchs, labeled *r.o.* and *c.l.n.*), it supplies the craniоventral and more mesial part of the plexus investing the cup. Early in this study, interest was aroused as to the identity and significance of this artery in its later form. For instance, it is much more conspicuous in embryos of 16 to 24 mm., particularly those sectioned sagittally (figs. 7, 8), and by this time is a small, dwindling, though strikingly constant branch of considerable length which courses ventrally, at least, as far as the base of the optic stalk. Fuchs' findings in the rabbit offered a clue to its identity. Its origin was traced back to a 5.5-mm. embryo (no. 3960, described above) in which the arterial supply to the primitive stalk, cup, and lens could be identified with a considerable degree of certainty. It was seen again in more advanced form in three embryos of a later age group (nos. 617, 163, 1121, from 7 to 11.8 mm.). Since the cranial division of the internal carotid at this stage curves closely around the short

optic stalk, the primitive ventral ophthalmic artery is also short and passes directly caudally for only a slight distance to reach the plexus on the mesial face of the optic cup (fig. 4*a*). In following through successive stages, it is clear that with the growth of the forebrain in one direction and the elongation and ventral shifting of the optic stalk and cup in the other, the origin of this artery and the area originally supplied by it become considerably withdrawn from each other. These changes are best understood by comparing figures 4 to 7 (see also fig. 13).

By the time the 18-mm. stage is reached, the primitive ventral ophthalmic artery has shifted to a course which is more ventral than caudal and has become considerably elongated in its course to the mesial and cranial aspect of the optic cup. In embryo no. 1390 of 18 mm. (fig. 7; fig. 33, pl. 3) the permanent stem of the ophthalmic artery has just appeared and clearly shows a common temporal ciliary branch to the caudodorsal aspect of the optic cup. The future common nasal ciliary branch of the ophthalmic artery cannot be definitely traced. The primitive ventral ophthalmic branch of the carotid, however, courses to the anterior margin of the optic stalk, which it accompanies beneath the cartilage primordium that is now beginning to separate the cranial and orbital cavities. At this stage there probably exists within the orbit at least a plexiform anastomosis between the stem of the ophthalmic and the primitive ventral ophthalmic artery, but the close association of ophthalmic veins in this region made positive identification impossible. In the next stage (seen in four embryos of 21 to 24 mm., figs. 8, 9) this elongated and dwindling primitive branch of the carotid is still present on both sides and appears to terminate definitely at the margin of cartilage around the optic nerve. Furthermore, a common nasal ciliary branch of the ophthalmic artery has now appeared. It is in the same position as the distal end of the primitive ventral ophthalmic artery, which has obviously just been annexed by the stem of the ophthalmic artery (insert, fig. 33, pl. 3). This anastomosis, taking place ventral to the optic nerve, is usually with the hyaloid branch of the ophthalmic stem (see below) and is followed by interruption of the primitive ophthalmic branch of the carotid just proximal to the secondary anastomosis. The remaining carotid remnant of the primitive ventral ophthalmic artery, so constantly seen at the 20-mm. stage, was not identified in two older embryos of about 40 mm. It is probable, however, that remnants of both the primitive ventral and dorsal ophthalmic arteries are frequently retained in the adult as minute branches to the region of the optic chiasm. Detailed illustrations of the arteries from the anterior circle of Willis in several mammalian forms (Hofmann, 1900; Wislocki and King, 1936) and in the human adult (see drawing of the arteries of the hypophyseal region in a pregnant woman, fig. 6 of Wislocki and King) suggest this assumption. Similar branches were also noted by the writer in a 5-month fetal brain injected by Professor Max Brödel.

It is not until the 12- to 14-mm. stage that an internal carotid branch entering the mesial end of the fetal ocular cleft may be identified for the first time. This definitive hyaloid artery branches from the elongated primitive dorsal ophthalmic artery, which now courses caudoventrally before reaching the dorsal aspect of the eye and is recognizable as the common temporal ciliary artery (fig. 5). Although both hyaloid and temporal ciliary arteries are present, it is important to note that the carotid origin of their parent stem is not that of the unequivocal adult stem of the ophthalmic artery, which first appears in the succeeding stage; instead, it still arises slightly caudal or proximal to the origin of the posterior communicating artery (fig. 5; figs. 40, 41, pl. 4). It is apparent that the primitive dorsal ophthalmic artery, which at an early stage entered the outer or lateral end of the fetal ocular depression after coursing over the dorsal margin of the optic cup, and was next observed, during the 7- to 12-mm. stages, to supply this region only through an intermediate capillary plexus on the cup, is the same artery which now sends a direct branch to the mesial end of the fetal ocular cleft. However, details of the secondary anastomoses and differentiation (comparable with those described for the rabbit by Fuchs) which bring about this result were not observed. This temporary ophthalmic artery, which is still primitive both in origin and in course, now resembles the permanent stem of the internal ophthalmic of the rabbit at an analogous stage (Fuchs' fig. 27). As was described above, Fuchs showed that the adult stem of the internal ophthalmic artery in the rabbit is represented early and first supplies the

choriocapillaris and ring artery, and thus indirectly the lens. Later, coincidently with its acquisition of hyaloid and temporal ciliary branches, the destination and course of the same artery are modified in keeping with the growth changes of brain, optic stalk, and eye. Three stages of this process were diagramed in his text figure 2 (p. 106). This illustration makes it clear that the stem of the internal ophthalmic retains its primitive carotid origin opposite the posterior communicating artery, which originally allowed a direct lateral approach to the dorsal part of the optic cup, and that it is, therefore, gradually forced by environmental changes to pursue a lengthening caudoventral as well as lateral course before it may develop the secondary anastomosis which annexes its hyaloid branch. Although the original stem of the ophthalmic artery is retained in the rabbit, it will be seen that in the human embryo it is replaced by a secondary artery which permits a more direct route to the area it supplies.

The stem of the ophthalmic artery at its adult point of origin was first identified in embryos of approximately 18 mm. Note in figure 7 that it arises from the internal carotid, lateral to Rathke's pouch, in a position which is caudoventral to the optic nerve and therefore far removed from the junction of the carotid with the posterior communicating artery. Both hyaloid and common temporal ciliary branches are present as in the preceding stage. It is obvious that this stem represents a caudal "migration" along the carotid of the primitive dorsal ophthalmic artery seen in the preceding stages. In embryo no. 1390 (18 mm.) and, more obviously, in one of the same stage (no. 144 of 16 mm.), there are dwindling carotid remnants in the position of the primitive dorsal ophthalmic artery, which position is, of course, well distal to that of the permanent ophthalmic stem (fig. 7). In no. 390, of 15.5 mm. (like no. 1390, in age group xix; injected by Brödel), the new stem of the ophthalmic artery, near its origin, could be seen to communicate with two of these distally placed and somewhat plexiform carotid branches which spread toward the root of the optic nerve. On one side of a younger embryo of 12.5 mm. (fig. 5) the primitive dorsal ophthalmic leaves the carotid very close to the posterior communicating artery, but it is more proximally placed on the other side. In another embryo of 11.5 mm. (fig. 40, pl. 4), which is somewhat more advanced in general, the artery on both sides is even farther removed from the junction of the posterior communicating artery and, therefore, closer to its adult origin. But in both these embryos the course of this primitive stem of the ophthalmic artery is devious. Since its origin is still nearer to that of the posterior communicating artery than to the base of the optic stalk, the artery is forced to proceed caudally for some distance before swinging ventrolaterally to reach the fetal ocular cleft. In three other embryos of 12 to 14 mm. (nos. 940, 511, and 899) the ophthalmic arteries are still plexiform and primitive in that no one vessel can be traced to the fetal ocular cleft on either side. Apparently the early postbranchial period is one of varying adjustment concerning arterial supply to the eye. As referred to in connection with the lengthening and dwindling of the primitive ventral ophthalmic artery (common nasal ciliary artery of the rabbit), the growth changes in brain and eye force a considerable separation of the carotid origin of the primitive ophthalmic arteries from the territory that they supply. Comparing the illustrations of human embryos with those of the rabbit (in which the internal ophthalmic artery of the adult retains its primitive origin opposite the posterior communicating artery; see Fuchs' fig. 27, 29), one sees that the interval of separation becomes relatively much greater in the human form. Because of the far greater expansion of the cerebral hemispheres in man, which draws the arteries radiating from the circle of Willis dorsally and finally caudally, there is a gradual elimination of the unfavorable primitive origin of the ophthalmic artery. It appears to be gradually "pulled along" the internal carotid in a movement similar to the migration of the dorsal segmental and visceral branches along the aorta. In the case of the ophthalmic artery there is evidence that the vessel moves along the parent artery by means of a series of anastomotic loops (a process called anastomotic progression by Streeter, 1918, in reference to other vessels), and that its ultimate stem represents a secondary branch of the carotid which has annexed the branches of the primitive dorsal ophthalmic artery. Since the adult ophthalmic artery arises from the part of the carotid which is caudal to the optic nerve, it can most directly supply the fetal ocular cleft in the caudoventral aspect of the nerve.

Relation of the Ophthalmic Artery to the Supraorbital Division of the Stapedial Artery

Various stages leading to the formation of the permanent adult stem of the ophthalmic artery, including its optic branches (the hyaloid, temporal, and nasal common ciliary), have just been described. No orbital branches of the ophthalmic artery have appeared at the 16- to 18-mm. stage. But meanwhile, the supraorbital division of the stapedial artery has emerged; it was traced to the orbit for the first time in an embryo of 18 mm. (fig. 7). It is known from the work of Tandler (cited by Evans, 1912) that this artery becomes a part of the middle meningeal artery, whose stem of origin is represented by the common stem of the maxillomandibular division of the stapedial artery. It has also been noted in most textbooks of anatomy that a branch of variable size from the anterior division of the adult middle meningeal may either anastomose with the ophthalmic artery or, as a definite anomaly, give origin to the lacrimal and other orbital arteries. The embryonic developments behind such variations in man have not been described.

In an 18-mm. embryo (no. 1390), the supraorbital vessel could be traced to the area where the ophthalmic branch of the fifth nerve divides into supraorbital (or frontal) and nasociliary branches; more specifically, it appears to terminate between the two nerves in the area just cranioventral to the optic nerve (fig. 33, pl. 3). As described above in reference to this embryo (p. 245), the distal part of the primitive ventral ophthalmic branch of the carotid, which also passes to the cranioventral side of the optic nerve, is about to be annexed by the ophthalmic artery as its common nasal ciliary branch; this takes place through an anastomosis ventral to the optic nerve. The common temporal ciliary branch of the ophthalmic stem has been established at an earlier stage. The fact that the temporal ciliary and the hyaloid arteries are the primary branches of the ophthalmic stem, and the nasal ciliary a secondary branch, may well be confusing in view of Keibel's statement in chapter 16, page 238 of the Keibel and Mall *Manual of Human Embryology* (1912) that "the nasal a. ciliaris communis gives off the a. hyaloidea [though] in many cases the a. hyaloidea arises at the point of division of the a. ophthalmica." The history of formation and the final configuration of the three optic branches are, however, entirely compatible if one visualizes the embryonic topographic relations. The common temporal ciliary (primitive dorsal ophthalmic) artery, related to the caudodorsal border of the optic nerve and eye, gives off the hyaloid artery. The latter branch, penetrating the optic nerve, is, of course, situated between the temporal ciliary and the primitive ventral ophthalmic artery coming from the internal carotid to the opposing anteroventral aspect of the nerve and eye. Therefore, the subsequent anastomosis, whereby the ophthalmic artery annexes its nasal ciliary branch ventral to the nerve, would commonly be between this branch (distal end of the primitive ventral ophthalmic artery) and the nearest branch of the ophthalmic stem, namely the hyaloid artery. After the primitive ventral ophthalmic branch of the carotid is interrupted just proximal to this anastomosis, the hyaloid artery does appear to arise from the resulting common nasal ciliary branch of the ophthalmic artery (see insert, fig. 33, pl. 3).

In embryos of approximately 20 mm., the supraorbital branch of the stapedial artery forms an anastomosis with the ophthalmic artery (fig. 8). In no. 6202 (21 mm.; fig. 34, pl. 3) this new connection, dorsal to the optic nerve, is between the ophthalmic artery, just proximal to its three optic branches, and the branch of the supraorbital division which now accompanies the length of the nasociliary nerve. Before this stage, the ophthalmic artery supplied only the eye, the surrounding orbital territory being supplied by the stapedial artery as shown in figure 34, plate 3. In a generally more advanced embryo of 24 mm. (no. 632, injected by Evans) the configuration of the orbital arteries is more primitive and plexiform than in the 21-mm. specimen, and demonstrates an intermediate stage (fig. 35, pl. 3). Here, the optic nerve, at the origin of the three primary optic branches of the ophthalmic artery, is surrounded by an arterial ring, the components of which represent several secondary anastomoses. The less well defined ventral portion represents in part the anastomosis between the primitive ventral ophthalmic branch of the carotid and the ophthalmic stem—the anastomosis which forms the common nasal ciliary artery (described above). The dorsal part of the ring is larger and probably of more recent origin. It is the channel

whereby the future definitive ophthalmic artery is permitted to pass, as typically in the adult, from the ventral to the dorsal aspect of the optic nerve. As will be seen in the next stage, a small part of the more ventral portion of this arterial ring is normally destined to disappear; all other parts are retained in the final configuration. In this embryo one sees three orbital branches of the supraorbital division of the stapedial artery, which arise near the craniomesial aspect of the optic nerve, each accompanying a division of the ophthalmic nerve. They are the frontal, supraorbital, and anterior ethmoid arteries.

An embryo of 39 mm. (no. 6203, enlarged 25 times and therefore permitting considerable detail in the graphic reconstructions) was interesting because the right and left sides illustrate two further successive stages in the development of the ophthalmic artery (fig. 36, pl. 3). The supraorbital division of the former stapedial artery, whose stem is dwindling following annexation of its branches by the internal maxillary artery, is now represented by the middle meningeal artery coursing lateral to the Gasserian ganglion. Beyond the orbit the meningeal artery is prolonged in the dural covering of the brain by a collateral branch of the supraorbital division. The original orbital segment of the supraorbital division, just distal to this collateral, is now interrupted at the orbital margin (compare figs. 35 and 36, pl. 3). In brief, the more primitive connection between the stapedial (now middle meningeal) and ophthalmic arteries has now become obliterated. In addition to its frontal and supraorbital branches, formed at the last stage, the ophthalmic artery has been essentially completed by the acquisition of its lacrimal branch, which terminates at the primordium of the gland. When the somewhat more primitive arteries on the right side of this embryo shown in figure 36, plate 3, are compared with the preceding figure 35 (24 mm.), the origin of the lacrimal artery can be observed. It is obvious that at least its proximal part represents the strictly orbital segment of the supraorbital division of the stapedial artery, which first entered the orbit at the 18-mm. stage. In a common form of adult variation, the anterior branch of the middle meningeal artery gives off an anastomotic branch which enters the outer end of the sphenoid fissure (or a separate foramen), and joins the lacrimal artery. This retention of an embryonic channel is readily understood on comparing the configuration of the 20- to 40-mm. stages (pl. 3).

The less mature development of the ophthalmic arteries on the right side of the 39-mm. embryo also shows a retention of the arterial ring which formed around the optic nerve at the 20-mm. stage. The cranioventral part of the ring represents the secondary channel whereby the permanent stem of the ophthalmic artery annexed the primitive ventral ophthalmic artery to form its common nasal ciliary branch. The dorsal part is the still later secondary channel which joined the supraorbital division of the stapedial artery to the ophthalmic artery. As seen in figure 36, plate 3, the cranioventral segment of this arterial ring is interrupted on the more advanced left side of this embryo, resulting in a typically adult configuration. It is of interest to recall here that the adult ophthalmic artery, after entering the orbital cavity underneath the optic nerve, may keep to this ventral position (15 per cent of the cases noted by Wolff, 1933) instead of passing immediately up over the lateral and dorsal aspect of the nerve to give off all, or nearly all, of its orbital branches as typically. This variation obviously results from the interruption of a dorsal rather than ventral segment of the arterial ring around the embryonic optic nerve.

Finally, the embryo in figure 36, plate 3 gives the explanation for variations reported in the origin of the common nasal ciliary artery of the adult. This small vessel (or vessels) has been frequently noted as leaving the main stem of the ophthalmic artery after the latter has passed around to the dorsal side of the optic nerve. Such an origin is already seen on the left side of this embryo (no. 6203). On the other hand, Quain (1844, cited by Wolff) says that the nasal ciliary and central retinal arteries usually arise in common below the nerve. As may be seen in comparing the two sides in our embryo, either one origin or the other would be determined by the point at which the more ventral segment of the arterial ring around the optic nerve is interrupted. The central retinal (embryonic hyaloid) artery of the adult is the only branch which is invariably given off before the ophthalmic passes from the ventral to the dorsal aspect of the optic nerve. This small artery tends to be anchored by its early penetration into the fetal ocular cleft, which is always represented in the ventral surface of the nerve. In connection with the his-

tory of the common ciliary arteries and the site of the fetal ocular cleft, it should be remembered that there is both an apparent and a real rotation of the optic stalk and eye. The first is merely the result of the lifting of the embryo head off the chest so that the fetal ocular cleft, always in caudoventral position, is invariably represented in the more inferior aspect of the adult optic nerve (Wolff, 1933). The second is the actual change in direction of the optic nerves from their original lateral plane to the adult anterolateral plane, resulting in a gradually diminishing angle between the optic axes. It is then realized that the arteries originally supplying the opposing caudodorsal (also more lateral) and cranioventral (more mesial) aspects of the optic cup are brought around to the temporal (lateral) and nasal (medial) surfaces of the eye. These changes must be kept in mind in the identification of the developing common ciliary arteries of the embryo, which are important from the standpoint of orientation in early stages.

THE PRIMITIVE TRIGEMINAL ARTERY

Evans (1912), in describing the origin of the primitive internal carotid artery from the end of the first aortic arch, called attention to certain smaller, irregular "presegmental branches of the dorsal aorta," which he identified in three early human embryos (6 to 15 somites), noting that remnants were apparently present in the Ingalls 4.9-mm. embryo (1907). He spoke of these branches as "very transitory and attracting our interest chiefly because they represent the first vascular sprouts sent out by the dorsal aorta, which, directed towards the sides of the medullary tube, are directly responsible for the formation of the vena capitis medialis." Sabin (1917) established the fact that the so-called "vena capitis medialis" serves only temporarily as a vein for the head, and renamed this channel, which is closely applied to the hindbrain wall, the "primitive rhombencephalic vessel." She emphasized that it is essentially a neural vessel which disappears entirely in the development of an extensive capillary plexus out of which ultimately both arteries and veins arise. From this plexus are developed what she named the "bilateral longitudinal neural arteries" (precursors of the basilar artery), which "form as an anastomosis between all the neural arteries from the dorsal aorta extending from the carotid arteries at the base of the optic stalk to the tip of the spinal cord." Streeter (1918) also described this "primordial hindbrain channel" (primitive rhombencephalic vessel) as arising in association with "irregularly placed slender communications from the dorsal aorta in the hindbrain region." The present study has revealed one of these branches, henceforth to be referred to as the "primitive trigeminal artery," to be relatively constant and often of considerable prominence in the early human embryo.

Evans (1912, footnote p. 622) made brief reference to the "presegmental branches of the dorsal aorta" as reported in two vertebrates. Tandler (1902) found a row of them in the rat at the 3-mm. stage. In his figure 8, five branches are shown arising at regular intervals from the paired ("dorsal") aorta opposite the interrupted first aortic arch back to the primitive hypoglossal artery opposite the fourth arch. At the 5-mm. stage, according to his figure 14, the longitudinal neural artery ("cerebral vertebral") is apparently more or less continuous cranially with the posterior communicating artery and caudally with the hypoglossal artery. Remnants of three presegmental branches remain. The one opposite the dorsal remnant of the first aortic arch (mandibular artery) in the trigeminal region is still uninterrupted, thereby forming an accessory link between the internal carotid and the longitudinal neural arteries. De Vriese (1905) found two relatively constant vessels in the rabbit embryo in front of the temporary hypoglossal artery, one at the level of the otic vesicle, the other near the Gasserian ganglion. She mentioned the possibility of their being the homologues or vestiges of "cephalic segmental arteries" related to the fifth, eighth, and twelfth nerves. At the 4- to 5-mm. stage (her pl. 15, fig. 2; pl. 16, fig. 2), the caudal divisions of the internal carotid (future posterior communicating arteries), reinforced by the primitive "trigeminal" and "auditory" (otic) arteries and connected with cranial extensions of the primitive "hypoglossal" and first cervical segmental arteries, have formed parallel tracts in the hindbrain region. De Vriese called these vessels the "primitive spinal arteries," which, of course, are synonymous with both the "cephalic" or "cerebral vertebrals" of early writers (for instance, Evans, 1912) and the "longitudinal neurals" of Sabin (1917). As the basilar artery is formed, through the

consolidation of the bilateral neural arteries, the trigeminal, otic, and hypoglossal anastomoses dwindle (De Vriese, pl. 17, figs. 21–24; pl. 15, fig. 12). In the 7-mm. embryo shown in her plate 16, figure 29, only the trigeminal branch remains uninterrupted. Fuchs (1905) in his study of the eye vessels of the rabbit embryo also showed what is undoubtedly the same trigeminal "Verbindungsast" at an early stage (see illustrations of a model, his figs. 7, 8). Sabin (1917) noted that her plate 6 of a 29-somite chick "shows none of the primitive arteries which connect the primitive rhombencephalic vessel directly with the dorsal aorta," but that in the 7-mm. pig (her pl. 7) "it is very interesting that two of these original arteries still persist and take part in the formation of this new longitudinal artery." A branch, in the trigeminal region, connecting the first aortic arch with the primordial hindbrain channel is apparently also shown in Evans' injected 5.7-mm. pig (1912, his fig. 394). Congdon (1922) stated, "there can be little doubt, in the light of . . . observations . . . on the development of the longitudinal neural arteries in other forms, that all the cranial members of the segmental series, as far back as the first cervical, contribute by anastomosis to the formation of the longitudinal neural arteries" in the human embryo. In spite of such references, partly buried in the important studies just mentioned, no description of these vessels in the human embryo has appeared. According to our material, the small presegmental branch or branches in the otic region, and also the hypoglossal artery, are exceedingly transitory. But the role played by the trigeminal branch in the early stages of development of the neural and basilar arteries is a considerable one, and its late persistence may take a prominent form. In the course of this study the primitive trigeminal artery was first observed in two embryos of 11 and 14 mm., in which it constitutes a large anastomotic branch between the carotid and basilar arteries. For the purpose of tracing its development in an orderly manner, however, the following description begins with the earliest embryo in which it could be identified, and ends with its final disappearance.

The cephalic end of an embryo of 20 somites (no. 2053 of 3 mm., age group xi) was reconstructed graphically in right and left lateral and coronal views. Davis (1923), who modeled and described the whole embryo, noted that the first pair of aortic arches is complete and the second in formation. There are two branches springing from the first arch. The first branch, which represents the primitive internal carotid, runs cephalad and "communicates with deep and superficial head plexuses in the region of the optic vesicle. The second branch leaves the arch just lateral to the first and, passing dorsally, ends in similar plexuses adjacent to the trigeminal ganglion." This second branch is the earliest representation of what is here called the primitive trigeminal artery. As can be seen in figure 37, plate 4, and figure 43, plate 5, this bilateral dorsal branch arches just mesial to the trigeminal ganglion and communicates with the primordial hindbrain channel ("primitive rhombencephalic vessel" of Sabin). The primordial channel is also supplied by two or three slender, irregularly placed vessels in the otic region. An initial stage in the formation of the second part of the primary head vein is represented by a channel which is present on the left side only, in a position superficial to the eighth nerve, and is a derivative of the primordial hindbrain channel. This specimen is illustrative of the first stage of vascular development described by Streeter (1918), during which the primordial vascular system of the head is established.

This 20-somite embryo may be compared with one of 24 somites (age group xii) reported by Johnson (1917), which shows a branch almost certainly identical with the primitive trigeminal artery just described. In his illustration it originates from the first aortic arch just caudal to the primitive carotid and is labeled *a.cer.?*. Johnson writes that it "extends dorsally and medially and terminates in the region of the posterior end of the prosencephalon, a short distance behind the anterior end of the notochord. I am unable from the specimen or from other descriptions to identify this vessel with any degree of certainty, but presume that it gives rise to one of the cerebral arteries." Comparison of Johnson's figure 1 (showing the arteries) and figure 2 (showing the veins) in plate 5 indicates that this branch of the first aortic arch is undoubtedly connected with the primordial hindbrain channel as in our comparable embryo.[11]

[11] In accordance with the interpretation of writers preceding Sabin's paper in 1917, Johnson refers to all parts of the primordial hindbrain channel, which temporarily drains the brain at this stage, as "veins of the anterior cardinal system" (see his p. 102).

A second stage in the development of this trigeminal artery is seen in a 4-mm. embryo (no. 836; figs. 38, 39, pl. 4), in which the third aortic arch has just become complete, and which illustrates the first stage in the differentiation of supply and drainage channels of the head described by Streeter. One may now distinguish fragments of the paired longitudinal neural arteries being formed in the region of the future basilar artery. At the level of the Gasserian ganglion, opposite the mandibular artery, which has succeeded the first aortic arch, there is the primitive trigeminal artery identified in the preceding stage. It must be noted, however, that it now arises from the primitive internal carotid and terminates in a fragment of the longitudinal neural artery, and that these vessels represent, respectively, the paired aorta and the primordial hindbrain channel of the earlier 20-somite embryo. The trigeminal artery is somewhat plexiform on the right but is an unequivocal channel on the left. The primordial hindbrain channel has disappeared and the primary head vein has formed, showing a prominent ventral tributary (later the stem of the inferior maxillary vein). This vein courses just lateral to the arterial anastomosis between the internal carotid and longitudinal neural arteries in the trigeminal region, and represents the more superficial parts of the head plexus seen in the 20-somite embryo.

At the eighth nerve and otocyst, opposite the second aortic arch, there are two or three other bilateral and more slender communications between the paired neural arteries and dorsal aorta; these were also definitely noted in the 20-somite embryo (fig. 37, pl. 4). The bilateral neural arteries are in early formation on the ventral hindbrain wall, being more prominent in the otic and trigeminal regions, and difficult to trace in the areas beyond and between (figs. 38, 39, pl. 4). Caudally the neural artery is lost in a capillary bed at the level of the ninth nerve. The internal carotid at this stage terminates in a plexiform channel dorsal to the optic vesicle, and has not yet formed its cranial and caudal divisions. At the mesencephalon, there are plexiform fragments of the caudal division (the future posterior communicating artery), which later becomes the most cranial source of blood to the neural artery.

A later stage in the development of these arteries is well illustrated by a more advanced embryo of 4 mm. (no. 588; fig. 1). Here the fourth aortic arch is complete, the pulmonary arch is in formation, and the first two arches have been succeeded by the irregular, plexiform mandibular and hyoid arteries. The primitive carotid, just ahead of the mandibular artery, bifurcates into two branches of equal caliber. One is the cerebral prolongation of the carotid artery, extending mesiocranially to the prosencephalon. The other is the primitive trigeminal branch, which arches laterally, dorsally, and then mesially to join the longitudinal neural artery (fig. 44, pl. 5). The neural arteries, which later consolidate to form the basilar artery, are more advanced than in embryo no. 836. They border a mid-line nonvascular strip on the ventral hindbrain wall and are everywhere connected laterally with the plexus enveloping the hindbrain; their extent is without interruption from the trigeminal region to the first cervical segmental arteries. The internal carotid has formed its primary cranial and caudal divisions, but the caudal one (future posterior communicating artery) dwindles into a capillary plexus at the mesencephalon, and no definite connection between it and the neural artery can be traced on either side. The chief supply to the neurals, as this specimen makes clear, is through the trigeminal arteries. On the right side of the embryo the trigeminal branch, in relative size, direction, and regularity of contour, actually appears to be the direct continuation of the carotid artery. One small connection between the carotid and neural arteries at the otocyst remains on the left side, and the primitive hypoglossal artery is interrupted on the right. In early stages, therefore, the bilateral longitudinal neural artery is supplied largely by the trigeminal artery; this supply is reinforced caudally by other more transitory presegmental branches of the paired (dorsal) aorta (or internal carotid) and also by the first cervical segmental artery.

Embryo no. 1380 of 5.5 mm., which is similar in general cranial development to that of 4.9 mm. described by Ingalls and also to our embryo no. 2841 (fig. 2), shows a somewhat later stage in the history of the primitive trigeminal artery. The definitive posterior communicating artery has just been formed by the union of the caudal division of the carotid (which it represents in greater part) with the bilateral longitudinal neural artery; however, this secondary anastomosis at the mesencephalon is relatively small and irregular. The trigeminal artery, though smaller on

the left side than on the right, still appears to be the chief cranial source of blood supply to the hindbrain, since the neural artery into which it empties is at least twice as large on each side between the level of the Gasserian ganglion and the otocyst than cranially at the midbrain. There also persists a small bilateral anastomosis between the internal carotid and neural arteries just ahead of the eighth nerve on one side and farther back at the otocyst on the other; these primitive otic arteries were not seen at any succeeding stage in this series.

In two embryos of 5 and 9 mm., which are comparable to no. 2841 of 5.3 mm. (fig. 2) in that the basilar artery is being formed, the trigeminal artery is present in prominent form. Reference should now be made to figure 3 (no. 3960, 5.5 mm., age group xiv). Here the trigeminal artery, as in no. 2841, constitutes a caroticoneural anastomosis, but the carotid end is cranial to the basilar end. Furthermore, the fact that the carotid end is smaller than the basilar on the left, and is plexiform at the basilar on the right, suggests an imminent interruption at this junction. In contrast, both posterior communicating arteries are large and regular and join one of the largest areas of coalescence of the two neural arteries. The caudal termination of each neural artery at the first cervical segmental artery is small and plexiform. In summary, the neural arteries, in this embryo, are supplied primarily by the posterior communicating division of the carotid but are still being reinforced by the primitive trigeminal branches in a manner reminiscent of a stage in the rabbit embryo described by De Vriese.

Another naturally well injected embryo (no. 4782 of 9 mm., of the succeeding age group xv, which is less advanced than no. 163 of 9 mm., fig. 4*a*) shows another variation of the trigeminal artery, as well as a somewhat later stage in the formation of the basilar artery. This specimen has not been photographed, but, since it was sectioned coronally, it was feasible to draw a freehand millimeter reconstruction of the ventral view as an aid in study of the slides. The basilar artery is nearly complete from the posterior communicating artery to the posterior level of the fifth nerve and Rathke's pouch, containing in this cranial segment only two small islands, each at the point where a bilateral set of branches is given off; the caudal part is still plexiform. On the left side, the advanced cranial end of the basilar appears to be directly continuous with the trigeminal artery, which arches laterally and is then directed mesially to join the carotid. This outer curve of the channel and the level of its position, between Rathke's pouch and the fifth nerve root, is exactly the configuration in all the embryos just described (pl. 5). No trigeminal artery (caroticobasilar anastomosis) is present on the other side of this embryo, and it is probably significant that here the posterior communicating artery is twice as large as on the side where the anastomosis persists. In other words, the internal carotid supplies the basilar on the right side through its permanent posterior communicating branch, but on the left largely through its temporary trigeminal branch.

In two reconstructed embryos of the early postbranchial period (no. 544, 11.5 mm., and no. 940, 14 mm., age group xvii), the basilar artery is fully formed, although irregular and retaining an island at its caudal end. In each, the vertebral artery is also complete, albeit very irregular, and the common carotid has just become definitive owing to the obliteration of the paired aorta between the third and fourth aortic arches. In view of this relatively late stage in general arterial development, and as compared with other embryos of this stage, all the cerebral arteries of these two specimens must be considered unusually primitive (figs. 40–42, pl. 4). Both embryos have retained the trigeminal or caroticobasilar anastomosis in striking form. On the right in no. 544 (fig. 41), the anastomosis is actually between the carotid and vertebral arteries through a long vessel paralleling the basilar artery. This lateral vessel is a late retention of the channel, prominent in many younger embryos (figs. 3–6), which originally supplied the more lateral and caudal regions of the hindbrain. An uninterrupted remnant of this primitive lateral basilovertebral anastomosis is seen again in no. 940 on the right side (fig. 42). Here the trigeminal artery connects the carotid with both the basilar and vertebral arteries by means of this lateral channel.

Another point of interest illustrated in the base views of these embryos (pl. 4) is the small size of the posterior communicating artery at its terminal part, which joins the basilar artery; this is seen on the left side of the embryo in figure 41 and on both sides in figure 42. Furthermore, the somewhat primitive vertebral artery in both embryos is also small in the upper part, which constitutes a segment of the first cervical

segmental artery (fig. 40). In these cases it is clear that the basilar artery is still being largely supplied by the prominent primitive trigeminal branch of the carotid. Only on the right side of no. 544 (fig. 41), where the primitive trigeminal anastomosis between the carotid and basilar arteries is interrupted, is the posterior communicating artery characteristically large at its basilar end. These embryos in general show a relatively late persistence of the stage wherein the basilar, representing the bilateral neural arteries, receives most of its blood from the trigeminal branch of the internal carotid.

There are several factors initiating the development and retrogression of this temporary embryonic artery. Dr. Streeter, early in this study, suggested that its formation is related to the precosity of the fifth nerve ganglion, and it was found to be related to the mesial border of this nerve at all stages (see the six figures of pl. 5). The eighth nerve and otocyst also attract presegmental branches from the paired aorta to the primordial hindbrain channel, as seen in the 20-somite embryo of 3 mm. These small otic branches, however, unlike the trigeminal, are seen only in the 3- to 4-mm. stages during the development of the second aortic arch, opposite which they form (figs. 37, 38, pl. 4). As soon as the second aortic arch dwindles, the primitive hypoglossal and first cervical segmental arteries, which accompany the corresponding nerves, supply the caudal end of the neural arteries (fig. 1). The primary branches of the first aortic arch, namely the internal carotid and trigeminal arteries, which had the head start, so to speak, at the 3-mm. stage, are now firmly established. They arose to supply the areas then undergoing marked differentiation, the primitive carotid branch taking care of the forebrain and optic vesicles, the trigeminal artery going to the most cranial part of the hindbrain. The prominent trigeminal artery and the smaller, more transient otic and hypoglossal arteries are all certainly related to the development of the brain in the region of the corresponding cerebral nerves (and developing ear), as suggested by De Vriese.

As has been shown above, the trigeminal artery is consistently found during the period preceding the caudal extension of the primary caudal division of the internal carotid to the mesencephalon, coincident with the development of this region and the emergence of the third and fourth nerves. At this time a secondary anastomosis joins the caudal carotid division with a cranial extension of the longitudinal neural artery to form the definitive posterior communicating artery, which usurps the role of the trigeminal artery as a temporary communicating artery between the carotid and the arteries of the hindbrain. The completed posterior communicating artery lies in the direct path of the blood flow from the internal carotid, in contrast with the trigeminal artery, which by this time leaves the carotid at an angle approaching 90°. Asymmetrical rotation of the forebrain, which is often observed in embryos of this stage, may relatively widen the interval between the carotid and the base of the hindbrain or alter the relation between the origin and destination of the trigeminal artery and, therefore, be another factor in its eventual interruption. In one embryo (no. 1121 of 11.8 mm.) showing interrupted remnants of the anastomosis, the carotid end is well in front of the basilar, although they appear to be in line in the coronal view (fig. 45, pl. 5). In another embryo (no. 3960; fig. 3), described above, the carotid and basilar ends of the long unbroken but dwindling anastomosis are in the same relative positions as the remnants just mentioned. In other words, the trigeminal artery, in the stages immediately preceding its interruption, leaves the carotid at an acute angle which is the opposite of the original configuration in that its apex is pointed cranially instead of caudally; the artery, therefore, finally proceeds in the reverse direction to that of the blood flow in the parent carotid. In contrast, the two largest embryos of this series (12 and 14 mm.; pl. 4) which retain the anastomosis show the trigeminal artery leaving the carotid in a craniodorsal direction, as originally seen in the 4-mm. embryo (fig. 2).

Later on, the developing basal sphenoid cartilage is interposed in the area between the internal carotid and basilar ends of the primitive trigeminal artery. In the two embryos of 12 and 14 mm., which showed the temporary anastomosis in most conspicuous form, the consolidation of the mesenchyme in this region is just getting under way. Somewhat equivocal remnants of the anastomosis exist in several other embryos from 11 to 16 mm., but no definite uninterrupted channel was found beyond 14 mm. In a 23-mm. embryo (no. 966; fig. 47, pl. 5), where the basal cartilage is well advanced, there is a continuous but plexiform remnant on the left side; on the right, the dural fold,

extending dorsolaterally from the sphenoid, marks the terminal point of a basilar remnant. Again, in a 43-mm. embryo (no. 886; fig. 48, pl. 5), basilar remnants extend to the fifth nerve roots and ganglia only as far as the developing fold of dura.

In conclusion, attention is called to the striking adult anomaly which may result from a retention of the trigeminal or caroticobasilar anastomosis, as reported by more than a dozen writers. Quain (1844) pictured the anomaly in his atlas, and here the large anastomotic branch perforates the sphenoid bone. In De Vriese' case (1905; a 9-month fetus), as in that of Smith (1909) and others, the branch perforated the dura at the level of the posterior clinoid process. The cases in which the related basal arteries were described or illustrated (Quain; De Vriese; Hasenjäger, 1937) show a configuration comparable to that of the 11- to 14-mm. embryos just described. They are indicative of the embryonic stages when essentially all the hindbrain arteries are supplied by the trigeminal branch of the internal carotid system. For instance, the basilar artery, caudal to the anastomosis, and one or both vertebrals were relatively small, as were also the posterior communicating artery at its connection with the basilar on the side of the anastomosis. In Hasenjäger's case both posterior communicating arteries were absent, and there were other variations related to the anterior cerebral and vertebral arteries. This anomaly and others, pertaining to the arteries radiating from the circle of Willis, are noted and their embryonic derivations briefly discussed by the writer in a chapter of Dandy's 1944 monograph on intracranial arterial aneurysms (see composite diagram, his fig. 28).

SUMMARY

An analysis of important stages in the development of the cranial arteries in the human embryo, based on graphic reconstructions of 22 specimens of the Carnegie Collection, is presented. The most significant changes in arterial development take place earlier than the critical stages in the formation of the dural veins as described by Streeter (1918), and plate 1, showing eight successive steps in the adaptation of the arteries to cranial growth changes from 4 mm. to birth, may be compared with Streeter's well known figure (his pl. 1), after which it was patterned.

The embryonic stages which were chosen to illustrate the formation of the head arteries are correlated with the transformation of the aortic arches described by Congdon (1922), and the whole is summarized in table 1. As noted in the table, the internal carotid, the basilar, and the vertebral arteries are formed during the first three stages, respectively, which belong to Congdon's "branchial" period (approximately 4 to 12 mm.). The fourth stage (12 to 14 mm.) is a significant transitional period in reference to both the aortic arches and the cranial arteries. The last three "postbranchial" stages (16 to 40 mm.) show the emergence of all the adult arteries, or their permanent adult stems of origin, and the completion of the circle of Willis. The various steps in the development of the cranial arteries can be followed by comparing the correlated illustrations of embryos in both lateral and horizontal views which were graphically reconstructed for text figures 1 to 11 and modified or simplified for plates 1 and 2.

Like vascular development elsewhere, that of the head arteries is characterized by a gradual dwindling or elimination of certain vessels, originally prominent, which serve temporary needs, paralleled by the elaboration of others. The emergence of the internal carotid artery during the involution of the first two aortic arches (fig. 1); the consolidation of bilateral neural arteries of the hindbrain to form the basilar artery (figs. 2, 3); and the secondary anastomoses between the upper seven cervical segmental branches of the paired aorta, giving rise to the vertebral artery (figs. 4, 5), were described more or less fully by Congdon (1922). The present study has concentrated on the formation of the various carotid and basilar branches. For instance, the history of the anterior cerebral artery is of particular interest. The primitive internal carotid of the 4- to 5-mm. stage has two major divisions arising near the summit of the optic vesicle: the caudal division, which later constitutes the posterior communicating artery after anastomosis with the bilateral neural arteries which precede the basilar artery; and the cranial division, which curves cranioventrally around the base of the optic vesicle (fig. 1). Although this latter division has often been called the "anterior cerebral artery," only a small part of it is

represented in the adult vessel. The cranial division of the carotid at its terminal end constitutes for some time a primitive olfactory artery supplying first the olfactory area (figs. 1, 2) and later the nasal fossa (fig. 4) and cavity (fig. 7). From this primary division of the carotid several collateral branches arise during later stages; these are, first, the anterior choroidal, secondly the middle cerebral, and finally the major part of the anterior cerebral artery. During the early postbranchial phase (12 to 14 mm.), the large primitive olfactory arteries are drawn mesially toward each other as the nasal fossae become approximated at the mid-line. Each has developed a craniomesial collateral supplying the emerging olfactory nerve root (fig. 32, pl. 3). By 18 mm., the collateral branch, which is a component of the anterior cerebral artery, begins to overshadow the primary artery (fig. 7). During the 20-mm. stage, when the anterior cerebral extends up between the cerebral hemispheres, the primitive olfactory artery sends an offshoot to the anterior perforated substance (figs. 8, 10) and is frequently retained in the adult as a variable striate branch of the anterior cerebral artery. The more constant medial striate (Abbie, 1937) or recurrent artery of Heubner, which arises from the anterior cerebral at the level of the anterior communicating artery, is very conspicuous in the embryo after 20 mm. (figs. 8–10). It dates far back in phylogenetic history and, together with the variable remnant of the primitive olfactory artery, represents early embryonic stages when a component of the future anterior cerebral artery is limited to the olfactory region.

The posterior communicating artery, which represents the original caudal division of the primitive internal carotid, remains relatively large throughout all the stages in this series. Until the completion of the vertebral artery in the early postbranchial phase, it is the channel through which the internal carotid supplies all the arteries of the hindbrain. As seen in plate 1, it primarily extends caudocranially from carotid to basilar arteries and gradually swings through a 180° arc as a result of the growing predominance of the cerebral hemispheres over the rest of the brain.

The definitive posterior cerebral artery cannot be identified unequivocally in this series of embryos, but it must be noted that its adult stem of origin represents the most distal (caudal) end of the original posterior communicating artery, and is, therefore, represented very early (figs. 2–4). Its ultimate extension emerges by means of an elaboration of one of the large diencephalic or mesencephalic branches of the posterior communicating artery seen in the 7- to 40-mm. embryos (figs. 16–21, pl. 1). These arteries are, of course, small branches of the posterior cerebral artery in the adult, and, as is the case with the formation of the anterior cerebral artery, a collateral branch finally overshadows the primary artery.

Of the cerebellar arteries, only the superior cerebellar becomes definitive during this series, appearing in the late branchial phase (7 to 10 mm.), when it supplies the metencephalon (fig. 4). However, the stems for both the inferior cerebellar arteries, anterior and posterior, often become recognizable among the numerous plexiform arteries which arise early to supply the region of the otic capsule and the myelencephalon (figs. 16–18, pl. 1). Not until a stage later than the present series, when the cerebellum surrounds the medulla, will the definitive destination of these arteries be established. In embryos between 20 and 40 mm., however, both arteries are represented by vessels which terminate in the large choroid plexus of the fourth ventricle (figs. 19, 20, pl. 1) which these arteries supply via small branches in the adult (fig. 11). Before the 40-mm. stage these arteries can usually be identified only tentatively as those which are larger and longer than numerous other associated basilar and vertebral branches which arise to supply the hindbrain regions, lying between the seventh and twelfth nerve roots massed in this area. Since these transverse branches are so often connected by longitudinal remnants of a prominent lateral channel (the primitive lateral basilovertebral anastomosis), paralleling the basilar artery and the cerebral part of the primitive vertebral artery, the arteries of the embryonic medulla long present a somewhat plexiform appearance (figs. 3–8). The variable origin in the adult of the anterior and posterior inferior cerebellar arteries, in contrast with the relative constancy of the superior cerebellar (Stopford, 1916), is thus readily explained (pls. 1, 2).

The external carotid system emerges in the early postbranchial period. As noted by Congdon (1922), the proximal end of the ventral pharyngeal artery, which succeeds the ventral parts of the first two aortic arches, is incorporated in the stem of the external

carotid artery (figs. 30–32, pl. 3). Its appearance coincides with the dwindling of the segment of paired aorta between the third and fourth aortic arches, which permits the third arch to become recognizable as the definitive common carotid artery (figs. 5, 6). The subsequent appearance of the various external carotid branches is illustrated in figures 7 to 11 (see also pl. 1) and discussed further in connection with the stapedial artery.

In the preparation of the outline covering the cranial arteries in general, three individual arteries merited special attention. Two of these, the temporary stapedial and the permanent ophthalmic, are interrelated and involved in a relatively prolonged series of modifications. Early stages in the formation of the stapedial artery, which originally pierces the stapes primordium and develops branches to the mandibular, maxillary, and supraorbital regions, have not heretofore been described in reference to the human embryo. As in many other vertebrates, the hyoid artery, which replaces the second aortic arch, is the carotid stem of the stapedial artery in man (figs. 1–4). Only the small root part of the hyoid artery, however, becomes incorporated in the stapedial artery, the greater part of the stapedial stem being a secondary cranial collateral of the hyoid vessel, which, by the late branchial phase (7 to 10 mm.), has assumed a relatively caudal course in the hyoid bar (fig. 4). By the early postbranchial phase, the proximal or carotid end of the hyoid artery appears to have been shifted from the caudal to the cranial level of the hyoid bar, where it gives off the stapedial collateral which passes craniocventrally into the mandibular bar to the mandibular nerve root, at the emergence of the chorda tympani nerve (figs. 5, 6; fig. 32, pl. 3). This phenomenon of arterial supply to the first pharyngeal bar by a vascular derivative of the second can be understood only by visualization of the unequal growth factors in the environment. The mandibular bar with its advancing maxillary process appears as though it pushed caudally the hyoid and glossopharyngeal bars, the components of which become closely approximated coincidently with the loss of definition between these originally well demarcated regions. These changes are illustrated in figures 30 to 32, plate 3, and also in plate 1, based on text figures 1 to 6.

It is of considerable interest that the stem of the stapedial artery forms an anastomosis, not with vascular remnants in the position of the dorsal part of the first aortic arch (as in the rat; Tandler, 1902), but with vessels which succeed the ventral part of that arch, namely, the ventral pharyngeal arteries (as in the rabbit; Fuchs, 1905). Unlike the corresponding vessel in the rat embryo, the dorsal or carotid end of the mandibular artery, which is the successor to the first aortic arch, gives rise to no appreciable branches and dwindles early. The major substance of the first or mandibular bar is supplied by the ventral pharyngeal artery (figs. 3, 4) throughout the branchial period, after which time the changed relations in the environment permit its distal end to be readily annexed by the stem of the stapedial artery (fig. 6; figs. 30–32, pl. 3).

At the height of its development (16 to 18 mm.) the stapedial artery has two primary divisions, the dorsal one passing far cranially to the supraorbital region in company with the ophthalmic branch of the fifth nerve, and the ventral one giving off two branches in association with the maxillary and mandibular roots of this nerve (fig. 7). During the 20-mm. stage the stem of the ophthalmic artery anastomoses with the supraorbital division of the stapedial (fig. 8) and eventually annexes the distal end of this artery to form its lacrimal branch (fig. 10; figs. 34–36, pl. 3). In like manner the external carotid artery, through its internal maxillary branch, annexes the maxillomandibular division of the stapedial artery at the mandibular nerve root to form the first part of the middle meningeal artery (figs. 8, 9). The second part of the middle meningeal represents the proximal part of the supraorbital division of the stapedial artery, which passes lateral to the Gasserian ganglion. Following these developments, the stem of the stapedial artery is interrupted at the stapes just distal to the original hyoid artery, which remains as the small caroticotympanic branch of the adult internal carotid; the remainder of the stapedial stem is the superior tympanic branch of the adult middle meningeal artery (fig. 8; fig. 35, pl. 3).

The formation of the definitive ophthalmic artery is both complicated and relatively late. The modifications of ophthalmic supply seen in the earlier stages of human embryos resemble those described in the rabbit by Fuchs (1905), but, in contrast, the late stages of the two species diverge markedly. The middle meningeal artery, representing the supraorbital

division of the stapedial artery, takes over most of the branches of the ophthalmic artery in the rabbit, whereas in man the ophthalmic artery annexes the distal end of the supraorbital division including all its orbital branches. Although not all complicated details in the formation of the ophthalmic artery were determined with certainty, essential features were revealed, and six stages are illustrated in figure 13.

For a relatively long period (4 to 18 mm.) the arteries to the human eye come from a part of the internal carotid which is considerably distal to the origin of the adult ophthalmic artery. In an early stage (3 to 4 mm.) the primitive internal carotid artery, near the point of its primary cranial and caudal divisions, gives off several short branches to the mesial face of the large optic vesicle (figs. 1, 2; figs. 38, 39, pl. 4), the base of which is supplied by a transitory (hypophthalmic) branch of the primitive maxillary artery (fig. 3*b;* fig. 44, pl. 5). Soon the primitive maxillary artery, confined medially along the neck of Rathke's pouch, loses all direct connection with the optic region (figs. 2, 13*a;* fig. 45, pl. 5). In embryos between 4 and 6 mm., most of the primitive eye, including the dorsal aspect of the optic vesicle, now undergoing differentiation, and the ectodermal lens pit, is supplied by a long carotid branch which arises opposite the posterior communicating artery and dips into the depression representing the fetal ocular cleft (figs. 3, 13*a*). In contrast with an opposing artery to be noted presently, the origin and destination of this artery, relative to the eye in all early stages, is primarily dorsal, although also caudal and lateral, and its main stem becomes the common temporal ciliary artery; it was named for this study the primitive dorsal ophthalmic artery. Its stem, which was represented in the preceding stage (figs. 1, 2), becomes even more prominent in the late branchial period (7 to 12 mm., fig. 4), at which time it takes a direct lateral course to the dorsal aspect of the optic cup and is lost in a manifold plexus now enveloping it (a primitive choriocapillaris, fig. 13*b*). Although this dorsal ophthalmic artery cannot, therefore, be traced into the outer end of the fetal ocular cleft (choroid fissure), as in the preceding stage, the plexus which it supplies, including an annular vessel around the periphery of the lens, is connected with a sinus-like vessel lying in the cleft mesial to the lens (primitive hyaloid vessel, fig. 13*b*)—a vessel which drains directly into the inferior maxillary veins. At this stage the more ventral, cranial, and mesial parts of the optic capillary mesh are supplied by another branch of the internal carotid which is here named the primitive ventral ophthalmic artery. It comes from the most distal and ventral segment of the internal carotid, opposite its anterior choroidal branch, which crosses the diencephalon (figs. 4, 13*b*). The definitive terms "ophthalmic" and "hyaloid" artery used by earlier writers in reference to vessels of this stage of the branchial period are therefore not justified. In the early postbranchial phase (between 12 and 14 mm.) the optic stalk further elongates, shifting the eye away from the brain wall and the internal carotid artery. As a result, both primitive ophthalmic arteries, dorsal and ventral, are drawn out in length; although their point of origin relative to the eye and the direction of their course is changed, the terminal area of each remains the same (compare figs. 4 and 5). Meanwhile the primitive dorsal ophthalmic artery has developed a direct branch to the lens through the mesial end of the fetal ocular cleft; this is the hyaloid artery, and the distal end of its parent artery is recognizable as the common temporal ciliary artery (figs. 5, 13*c*). Between 16 and 18 mm. these ocular branches are transferred to the permanent stem of the ophthalmic artery, which was first identified late in this stage (figs. 7, 13*d*). It is apparent that the ophthalmic artery, with its internal carotid origin caudal to the optic stalk and opposite Rathke's pouch, has finally reached this adult position by a considerable caudal (or proximal) migration along the carotid of the primitive dorsal ophthalmic artery which it represents; as noted above, this primitive artery arises opposite the posterior communicating artery, well cranial to the optic stalk. There is evidence that this movement is permitted by a succession of anastomotic loops (Streeter's "anastomotic progression") from the carotid during the postbranchial stage, when the expanding brain and cerebral arteries become more and more withdrawn from the developing optic nerve and eye. The condensation of mesenchyme in the position of the orbital roof, at the future optic foramen, completes the process of relegating the ophthalmic artery to its permanent carotid origin below the level of this structure. At this time the stem of the ophthalmic artery annexes the distal end of the attenuated primitive ventral ophthalmic artery, coming from the most dis-

tal segment of the internal carotid (opposite the anterior choroidal artery); in this manner is formed the common nasal ciliary artery (fig. 33, pl. 3). By the 20-mm. stage, therefore, all the ocular branches of the ophthalmic artery have been established.

The orbital branches which form the most conspicuous part of the adult ophthalmic artery are derivatives of the supraorbital division of the stapedial artery (fig. 13*d*). Through the formation of an arterial ring around the optic nerve during the 20- to 24-mm. stage (fig. 13*e*) and the subsequent interruption of a ventral segment of this ring (fig. 13*f*), representing usually a part of the secondarily formed common nasal ciliary branch of the ophthalmic stem, the ophthalmic artery is allowed to pass from the ventral to the dorsal side of the nerve, as in the adult, and becomes continuous with the supraorbital division of the stapedial artery. Sometime between 24 and 40 mm., the first, strictly orbital segment of the original supraorbital division, now part of the middle meningeal artery, becomes the stem of the lacrimal branch of the ophthalmic artery. Toward the end of this period, an interruption or dwindling of the original supraorbital division at the orbital margin, that is, between its proximal and distal parts, which now belong to the middle meningeal and lacrimal arteries respectively, leaves the ophthalmic artery recognizably identical with the adult configuration (fig. 13*e, f*; figs. 35, 36, pl. 3). The embryonic connection between the ophthalmic and stapedial arteries is frequently represented in the adult by a branch of variable size connecting the ophthalmic (commonly its lacrimal branch) and middle meningeal arteries at the lateral end of the sphenoid fissure.

Finally there is described the development of a conspicuous temporary artery which, in reference to the human embryo at least, has heretofore received no attention in the literature. This artery contributes extensively toward the formation of the bilateral longitudinal neural arteries which join to form the basilar artery, and because of its position has here been named the primitive trigeminal artery. The first representation of this trigeminal vessel was found in a 20-somite embryo of 3 mm., in which there are two definite branches from the paired (dorsal) aorta at its point of junction with the first aortic arch (fig. 37, pl. 4). One of these is the primitive internal carotid artery, which extends to the optic vesicle at the forebrain. The other is the primitive trigeminal artery, which leaves the aorta just caudal to the carotid branch, and arches dorsally toward the fifth nerve ganglion (fig. 43, pl. 5). The trigeminal artery at this stage supplies the cranial end of the primordial hindbrain channel, from whose proliferating endothelium the arteries (for instance, those which precede the basilar) and veins of the hindbrain wall are subsequently derived.

In the next stage (4 to 5 mm.) the bilateral longitudinal neural arteries, which are destined to form the basilar artery, emerge as derivatives of a plexus which earlier resulted from differentiation of the primordial hindbrain channel (figs. 38, 39, pl. 4; fig. 1). The cranial end of each neural artery is supplied by the trigeminal artery, which, following the involution of the first two aortic arches, is now considered a branch of the primitive internal carotid artery. Development of the diencephalic and mesencephalic regions at this time is accompanied by an extension of the primary caudal division of the internal carotid artery (fig. 1). Not until it has developed a secondary anastomosis with the cranial end of the neural artery, however, does the caudal division of the carotid become the definitive posterior communicating artery (fig. 2). Until this time the trigeminal branch of the internal carotid is the major source of blood to the longitudinal neural artery of the hindbrain, the caudal connections of which with the transitory hypoglossal artery and the first cervical segmental artery are typically small. Subsequently, the bilateral neural arteries consolidate to form the basilar artery. Concomitantly or soon thereafter, the posterior communicating artery takes over from the trigeminal artery the role of supply to the arteries of the hindbrain during the remainder of the branchial period.

Following the establishment of the posterior communicating artery (an important channel in the embryo in contrast with its subsidiary role in the adult circle of Willis), the trigeminal artery usually dwindles. In certain embryos, however, the primitive trigeminal branch persists for varying periods after the formation of the posterior communicating and basilar arteries, producing a prominent caroticobasilar anastomosis (figs. 40–42, pl. 4). In such cases the posterior communicating artery, in the terminal part connecting it with the basilar artery, was found to be relatively small. No large trigeminal or caroticobasilar anastomosis was identified beyond the early post-

branchial period, when the formation of the vertebral artery relieves the internal carotid of its earlier role of supply to all the arteries of the hindbrain. Other factors contribute to the elimination of the trigeminal anastomosis; namely, unequal environmental growth with consequent shifting in the relative position of the carotid and basilar ends of the anastomosis, which opposes its course to that of the current in the internal carotid; and the interposition of the basal sphenoid cartilage between the carotid and basilar ends during the 12- to 20-mm. stages. Interrupted remnants, particularly of the basilar end of the anastomosis, were identified in several embryos up to 40 mm. (figs. 47, 48, pl. 5). The occasional persistence of the primitive trigeminal artery in the adult, like that of several other arteries which serve temporary embryonic needs, may result in a significant adult anomaly not infrequently reported in the literature—an anastomotic branch of considerable size between the basilar artery and the intracavernous part of the internal carotid.

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LIST OF ABBREVIATIONS IN FIGURES

ant. card. v., anterior cardinal vein
ant. cerebr. a., anterior cerebral artery
ant. choroid. a., anterior choroidal artery
ant. commun. a., anterior communicating artery
ant. ethm. a., anterior ethmoid artery
ant. inf. cerebel. a., anterior inferior cerebellar artery
ant. perfor. subst., anterior perforated substance
ant. spin. a., anterior spinal artery
aort. arch, aortic arch
arter. tr., arterial trunk
axil. a., axillary artery
bas. a., basilar artery
bilat. long. neur. a., bilateral longitudinal neural artery
brach. a., brachial artery
carot.-bas. anast., caroticobasilar anastomosis
carot.-tymp. a., caroticotympanic artery
caud. divis., caudal division
cent. a. of ret., central artery of retina
choroid. plex., choroidal plexus
chord. tymp. n., chorda tympani nerve
com. nas. cil. a., common nasal ciliary artery
com. temp. cil. a., common temporal ciliary artery
cran. divis., cranial division
dienceph. a., diencephalic artery
dist., distal
duct. art., ductus arteriosus
ext. carot. a., external carotid artery
ext. max. a., external maxillary artery
fetal ocul. cleft, fetal ocular cleft
first cerv. segm. a., first cervical segmental artery
first cerv. mesoblast. segm., first cervical mesoblastic segment
front. a. (n.), frontal artery (nerve)
hyal. a., hyaloid artery
inf. alveol. a., inferior alveolar artery
inf. hypoph. a., inferior hypophyseal artery
infraorb. a. (n.), infraorbital artery (nerve)
innom. a., innominate artery
int. aud. a., internal auditory artery
int. carot. a., internal carotid artery
int. mam. a., internal mammillary artery
int. max. a., internal maxillary artery
lacrim. a., lacrimal artery
ling. a., lingual artery
mand. a., mandibular artery
max.-mand. div., maxillomandibular division
med. a. of corp. cal., median artery of corpus callosum
med. str. a. (recur. a.), medial striate artery (recurrent artery of Heubner)
mesenceph. a., mesencephalic artery
metenceph. a., metencephalic artery
mid. cerebr. a., middle cerebral artery
mid. mening. a., middle meningeal artery
nas. fossa, nasal fossa
nasocil. n., nasociliary nerve
occip. a., occipital artery
olf. area, olfactory area
ophth. a., ophthalmic artery
opt. ves., optic vesicle
ot. ves., otic vesicle
paired aort., paired aorta
pharyng. bar, pharyngeal bar
post. auric. a., posterior auricular artery
post. cerebr. a., posterior cerebral artery
post. choroid. a., posterior choroidal artery
post. commun. a., posterior communicating artery
post. inf. cerebel. a., posterior inferior cerebellar artery
post. spin. a., posterior spinal artery
prim. head v., primary head vein
primit. otic a., primitive otic artery
primit. dors. ophth. a., primitive dorsal ophthalmic artery
primit. hypoglos. a., primitive hypoglossal artery
primit. lat. bas.-vert. anast., primitive lateral basilovertebral anastomosis
primit. max. a., primitive maxillary artery
primit. olf. a., primitive olfactory artery
primit. trigem. a., primitive trigeminal artery
primit. vent. ophth. a., primitive ventral ophthalmic artery
primord. hindbr. channel, primordial hindbrain channel

primord., primordium
pulm. a., pulmonary artery
remn., remnant
second. anast., secondary anastomosis
som., somite
staped. a., stapedial artery
subcl. a., subclavian artery
supfic. petros. n., superficial petrosal nerve
supfic. temp. a., superficial temporal artery
sup. cerebel. a., superior cerebellar artery
sup. hypoph. a., superior hypophyseal artery
sup. thyr. a., superior thyroid artery
sup. tymp. a., superior tympanic artery
supraorb. a. (n.), supraorbital artery (nerve)
supraorb. div., supraorbital division
thyr.-cerv. tr., thyrocervical trunk
tymp. n., tympanic nerve
ventr., ventricle
vent. pharyng. a., ventral pharyngeal artery
vert. a., vertebral artery

Adaptation of the cranial arteries to growth of the brain and head from 4 mm. to birth. (Modified from text figs. 1–11.)

FIG. 14. (Embryo no. 588, 4 mm.) The primitive internal carotid supplies the forebrain through its cranial and caudal divisions and its primitive maxillary branch, and supplies the hindbrain through the primitive trigeminal branch which joins the cranial end of the bilateral neural artery. The caudal end of the neural artery is fed by the primitive hypoglossal and first cervical segmental arteries. Hyoid and mandibular arteries have succeeded the first two aortic arches.

FIG. 15. (Embryo no. 2841, 5.3 mm., supplemented by no. 3960, 5.5 mm.) The caudal division of the internal carotid has become the definitive posterior communicating artery following anastomosis with the bilateral neural artery, which is consolidating with its mate of the opposite side to form the basilar artery. The primitive trigeminal and hypoglossal arteries are dwindling. The substance of the first two pharyngeal bars is supplied by the ventral pharyngeal artery reinforced by the hyoid artery.

FIG. 16. (Embryo no. 163, 9 mm.) The vertebral artery is being formed by transverse anastomoses between each of the upper seven cervical segmental arteries, but all cerebral arteries are still supplied primarily by the internal carotid. The stem of the hyoid artery lies at the cranial level of the hyoid bar, and its course is more caudal, corresponding to the caudal swing of the seventh nerve. The third pharyngeal bar with its nervous and arterial components is no longer a separate entity. The ventral pharyngeal artery, skirting the mandibular end of the chorda tympani nerve, terminates at the mandibular nerve root. In addition to the primitive dorsal ophthalmic artery of preceding stages, a primitive ventral artery supplies the plexus investing the optic cup and lens.

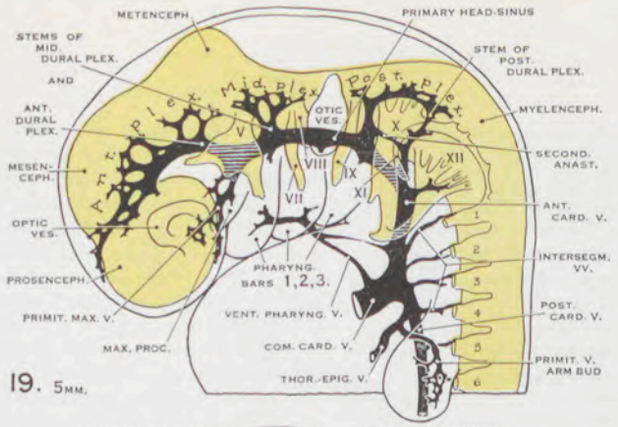
FIG. 17. (Embryo no. 1771, 12.5 mm.; details of stapedial artery from nos. 940 and 6258, each 14 mm.) In this early postbranchial phase, the hyoid artery, now no longer readily identified with its corresponding pharyngeal bar, gives off the stapedial branch, which descends into the mandibular substance and joins the distal remnant of the ventral pharyngeal artery, whose proximal end represents the stem of the external carotid. Dwindling of the paired aorta between the third and fourth aortic arches permits recognition of the common carotid, and the subclavian origin of the vertebral artery is being shifted cranially. The primitive dorsal ophthalmic artery has definitive hyaloid and temporal ciliary branches.

FIG. 18. (Embryo no. 1390, 18 mm.) The stem of origin of most cerebral arteries and external carotid branches is typically adult. The primitive olfactory artery, which constituted the terminal end of the cranial carotid division in all earlier stages, is dwindling in favor of its anterior cerebral collateral. The stapedial artery has two divisions, comprising three branches, which supply the orbital, maxillary, and mandibular regions. The adult stem of the ophthalmic artery is present for the first time, having annexed the ocular branches of the dwindling primitive dorsal and ventral ophthalmic arteries. The vertebral artery is fully formed, and its parent subclavian artery now arises opposite the pulmonary arch.

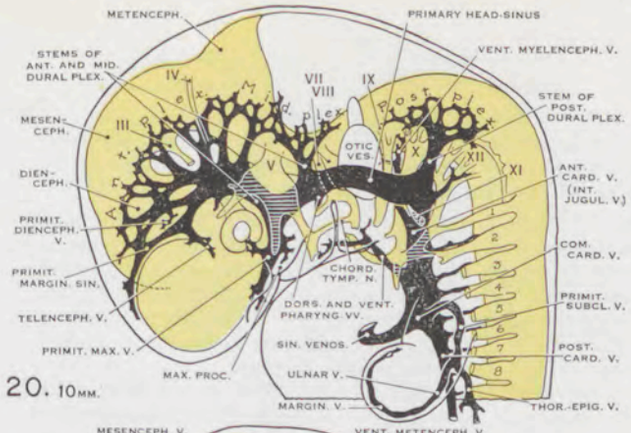
FIG. 19. (Embryo no. 632, 24 mm.) The expanding cerebrum is responsible for the medial prolongation of the anterior cerebral arteries, which are now joined by the anterior communicating artery. The stem of the stapedial artery has dwindled following two secondary anastomoses: the ophthalmic artery has annexed its supraorbital division and the internal maxillary its maxillomandibular division, permitting the last named to become recognizable as the stem of the middle meningeal artery.

FIG. 20. (Embryo no. 886, 43 mm.; details of certain arteries from no. 6203, 39 mm.) With further development of the cerebrum, the posterior communicating branch of the carotid has nearly completed its swing from the caudocranial direction to the reverse. The stems of the anterior and posterior inferior cerebellar arteries, long concealed in remnants of the primitive basilovertebral anastomosis (figs. 16, 17), are recognizable and terminate in the choroid plexus of the fourth ventricle. The large choroid plexus of the lateral ventricle is supplied not only by the anterior and posterior choroidal arteries, but also by a temporary primitive branch of the anterior cerebral artery at the foramen of Monro. The ophthalmic artery has acquired its lacrimal branch, which represents part of the supraorbital division of the stapedial artery; the remainder of this division is incorporated in the middle meningeal artery.

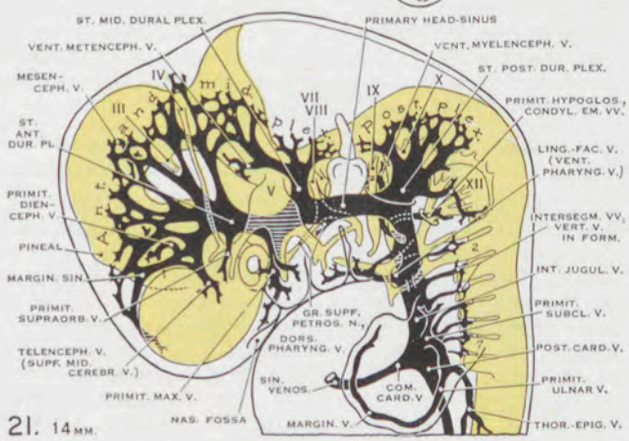
FIG. 21. The newborn (or adult) configuration. Note that the only essential difference between the adult cerebral arteries and those of the preceding figure is dependent upon the ultimate predominance of the cerebral and cerebellar hemispheres. The formation of the corpus callosum and fornix has intervened between the anterior cerebral artery and the diencephalon so that that artery no longer supplies the choroid plexus. The posterior cerebral artery has emerged as a development of one of the diencephalic or mesencephalic branches, which are relatively reduced in the adult. In like manner, the anterior and posterior inferior cerebellar arteries become definitive and supply the cerebellar choroid plexus merely en route to their adult destination. The three branches of the temporary stapedial artery are recognizable as the supraorbital, infraorbital, and inferior alveolar arteries.



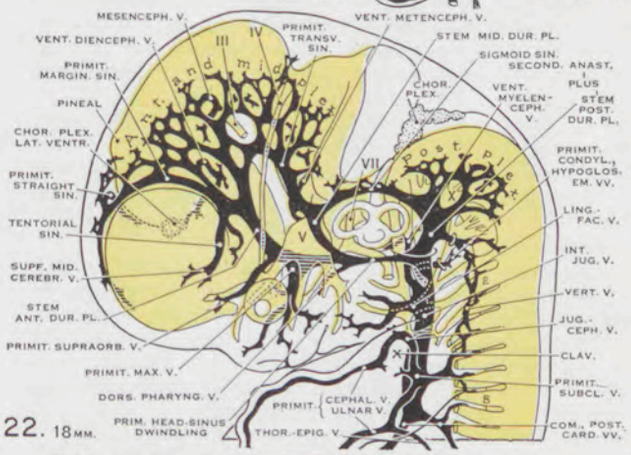
19. 5MM.



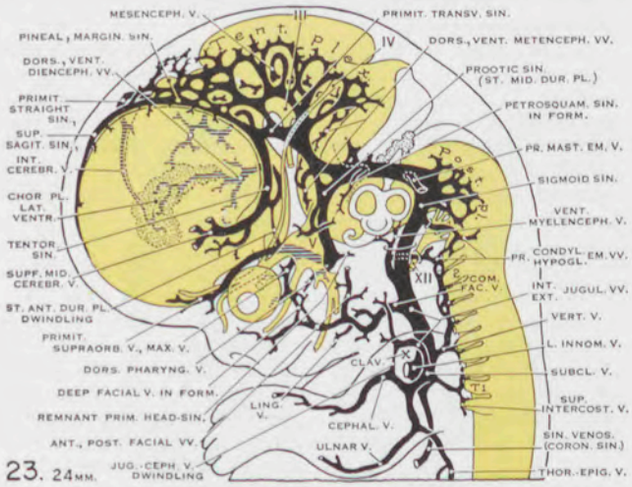
20. 10MM.



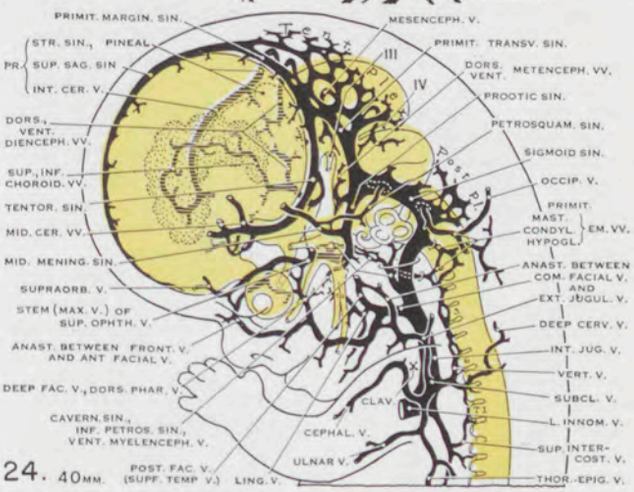
21. 14MM.



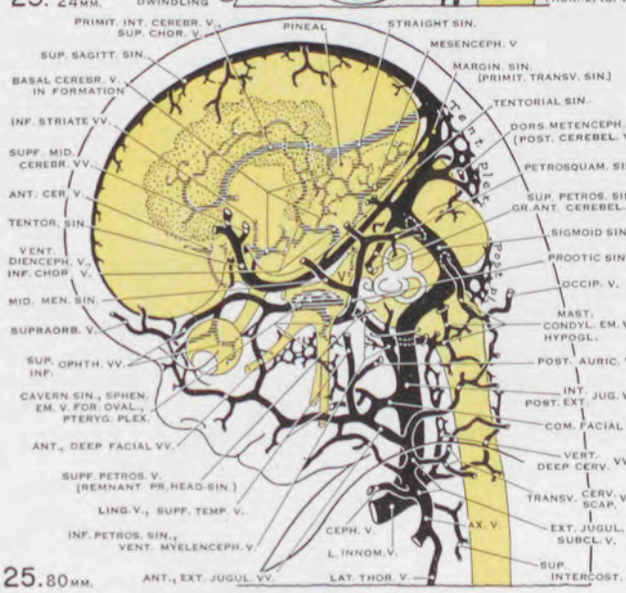
22. 18MM.



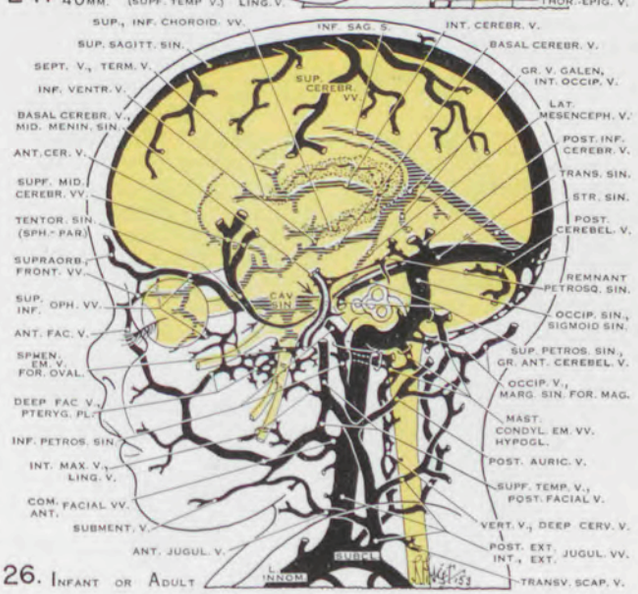
23. 24MM.



24. 40MM.



25. 80MM.



26. INFANT OR ADULT

Adaptation of the cerebral arteries to growth of the brain from 4 mm. to birth, and the formation of the circle of Willis. With one exception (fig. 24), these are the same embryos shown in plate 1 and are viewed from below so that the right side of the embryo is at the observer's left. (Modified from text figs. 1–11.)

FIG. 22. (Embryo no. 588, 4 mm.) Note that the internal carotid divides before reaching the forebrain; the dorsolateral branch is the temporary trigeminal artery, and the medioventral division is the permanent prolongation of the carotid skirting the margins of Rathke's pouch. The trigeminal artery supplies the bilateral longitudinal neural artery, and is reinforced by smaller presegmental branches of the carotid and paired aorta in the otic and hypoglossal regions.

FIG. 23. (Embryo no. 2841, 5.3 mm., supplemented by no. 3960, 5.5 mm.) The bilateral longitudinal neural arteries are consolidating to form the basilar artery and each is supplied by the new posterior communicating artery, which represents the caudal division of the carotid; the primitive trigeminal artery is dwindling. The cranial division of the carotid constitutes a primitive olfactory artery terminating at the olfactory plate.

FIG. 24. (Embryo no. 617, 7 mm., of the same stage as that shown in fig. 16, pl. 1.) The basilar artery is complete but irregular, with island formations. It is paralleled on either side by more or less continuous remnants of a channel (the basilovertebral anastomosis) which traverses the area between the mesial and lateral components of the sixth to twelfth nerve roots. The caudal ends of the posterior communicating arteries, terminating in the basilar artery, constitute the first parts of the posterior cerebrals.

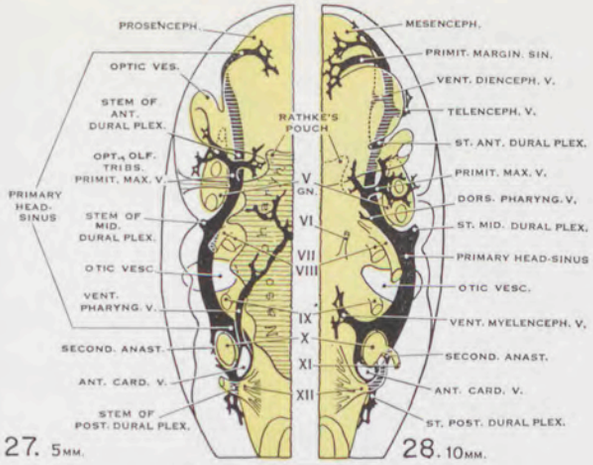
FIG. 25. (Embryo no. 1771, 12.5 mm.) The primitive olfactory artery has two branches, the original vessel terminating at the olfactory pit and a mesial branch going to the region of the primordial olfactory nerve root. Certain branches of the basilar and vertebral arteries are emerging from components of the basilovertebral anastomosis. The arterial ring around the sixth nerve, for instance, explains the variable origin of the basilar branches in this region during later stages and in the adult.

FIG. 26. (Embryo no. 1390, 18 mm.) The primitive olfactory artery supplies the nasal fossa through branches accompanying the olfactory root; but the artery is already overshadowed by its anterior cerebral collateral, which extends to a plexus at the mid-line. Note the different origins of the anterior inferior cerebellar and internal auditory arteries on the two sides in relation to the sixth nerve, and compare with figures 25 and 28. The new adult stem of the ophthalmic artery has annexed the primitive dorsal and ventral ophthalmic arteries which supplied the optic cup and lens in earlier stages.

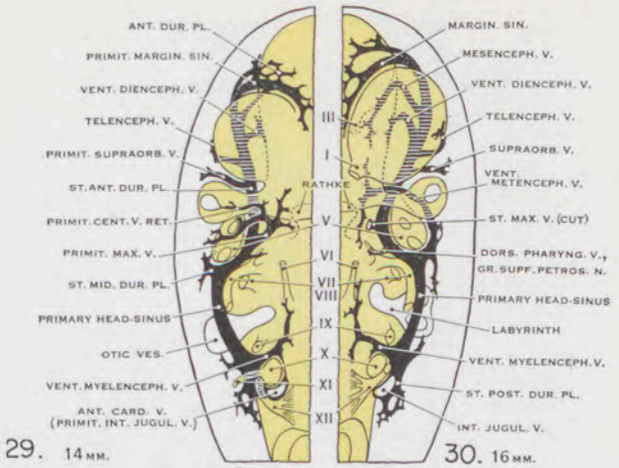
FIG. 27. (Embryo no. 632, 24 mm.) The circle of Willis is complete with the formation of the anterior communicating artery, which gives off a median branch supplying the commissural plate. Remnants of the primitive olfactory artery are incorporated in striate branches of the anterior cerebral artery which penetrate the anterior perforated substance.

FIG. 28. (Embryo no. 886, 43 mm.) In embryos less than two months old, the adult configuration of the circle of Willis and its radiating branches has become readily recognizable in the ventral view of the brain, as a result of the expansion of the cerebral hemispheres and the accompanying caudal swing of the posterior communicating artery. This artery remains relatively large during fetal life, preceding the late completion of its collateral posterior cerebral branch, which in most adult cases is supplied more by the basilar than by the internal carotid artery.

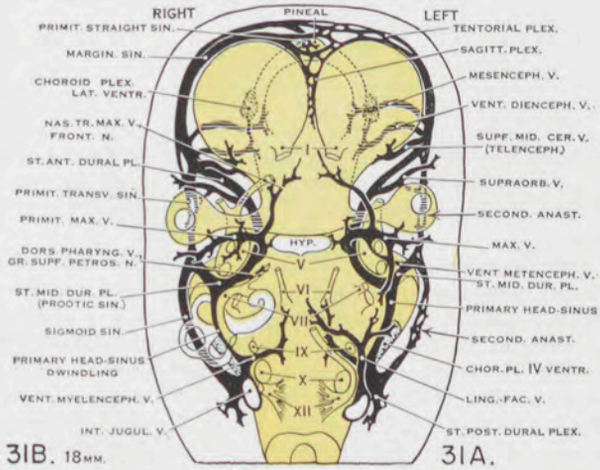
FIG. 29. Newborn configuration. Note that the origin of the anterior cerebral artery, which, in the adult, is commonly hidden by the parent carotid and its middle cerebral branch when the circle of Willis is viewed *in situ,* is distal to that of the anterior choroidal and posterior communicating arteries. The relation of these arteries to each other is clear when this figure is compared with the embryo. Frequent variation and asymmetry, in the arteries forming the posterior half of the circle of Willis, is the result of an incomplete transition to the adult predominance of the basilar over the internal carotid in supply to the posterior cerebral artery. The medial striate branch of the anterior cerebral, which varies considerably in size, is potentially significant.



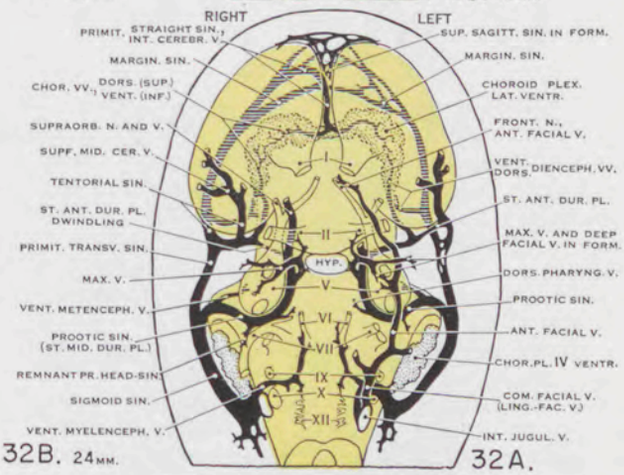
27. 5MM. 28. 10MM.



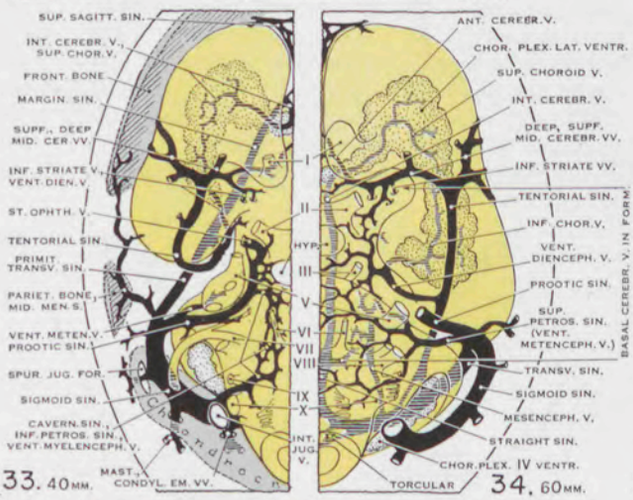
29. 14MM. 30. 16MM.



31B. 18MM. 31A.

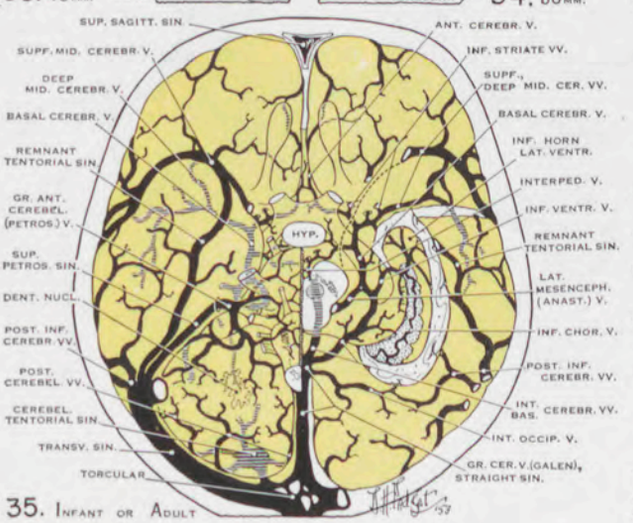


32B. 24MM. 32A.

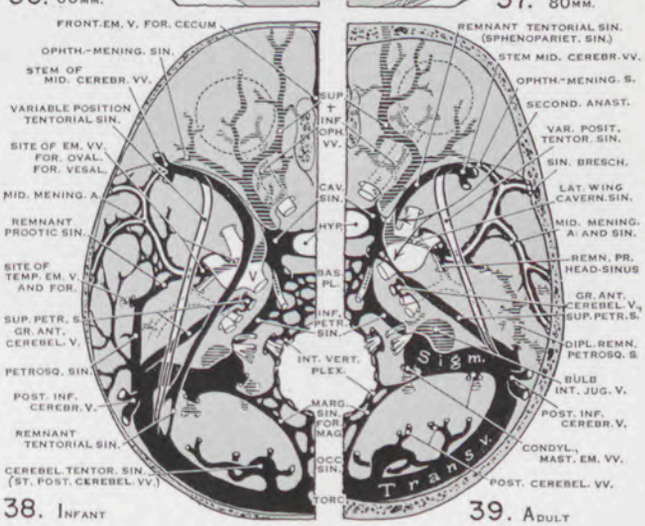


33. 40MM. 34. 60MM.

36. 60MM. 37. 80MM.



35. INFANT OR ADULT



38. INFANT 39. ADULT

Plate 3

Partial horizontal reconstructions of 7 embryos from 4 to 40 mm. (ventral view), to illustrate the environmental changes leading to the formation of the stapedial artery and the incorporation of its supraorbital division in the ophthalmic artery.

Fig. 30. (No. 2841, 5.3 mm. See lateral view in text fig. 2*a*.) In this embryo of the early "branchial" phase, there is a regular conformation of the cranial nerve roots and aortic arches to each pharyngeal bar and corresponding pouch. The area formerly occupied by the first and second aortic arches is now traversed by two vessels: the hyoid artery, representing the dorsal end of the second arch, and the ventral pharyngeal artery (terminating at the mandibular nerve root), in the general position of the ventral ends of both arches. Note that the dorsal end of the first aortic arch is represented by only a small remnant of the mandibular artery. ×30.

Fig. 31. (No. 617, 7 mm. See lateral view of same stage in text fig. 4*a*.) The third pharyngeal bar has lost definition and, coincidently with the development of the maxillary process and several collateral nerve roots, the fifth to the tenth cranial nerves appear to be bunched together, and the seventh nerve has begun to swing caudally. Note that the carotid origin of the hyoid artery, near the caudal border of the corresponding pharyngeal bar in the previous stage (fig. 30), is now at the level of the cranial border. ×21.6.

Fig. 32. (No. 940, 14 mm.; distal connections of stapedial artery superimposed from another 14-mm. embryo, no. 6258. See lateral view of this reconstruction in text fig. 6.) This embryo is emerging from the "branchial" phase, and the carotid stem of the hyoid artery no longer appears to be within the hyoid bar, but is cranial to the first pharyngeal cleft. These altered relations readily permit the stapedial collateral of the hyoid artery to annex the distal remnant of the ventral pharyngeal artery at the mandibular nerve root, thereby forming the primary maxillomandibular division of the stapedial artery. ×15.

Fig. 33. (No. 1390, 18 mm. Other illustrations in text fig. 7.) The upper supraorbital division of the stapedial artery, whose stem was formed in the preceding stage (fig. 32), passes into the primitive orbit as far as the division of the ophthalmic nerve root. The stem of the ophthalmic artery (earlier stages shown in text fig. 13) has formed two of its primary ocular branches from the primitive ophthalmic arteries, and is about to annex the third, as shown in the diagrammatic insert. ×15.

Fig. 34. (No. 6202, 21 mm.) The supraorbital division of the stapedial artery has formed two orbital branches accompanying the frontal and nasociliary branches of the ophthalmic nerve. The artery could not be traced into the orbit on the left side of the embryo; on the right, however, it has joined the stem of the opththalmic artery dorsal to the optic nerve and has, therefore, completed a developmental phase shown in the generally more advanced embryo of the succeeding figure 35. ×15.

Fig. 35. (No. 632, 24 mm. See lateral view in text fig. 8*a*.) This embryo shows how the ophthalmic artery gains the dorsal side of the optic nerve and acquires its orbital branches. The arterial ring surrounding the optic nerve permits the supraorbital division of the stapedial artery, which now has three branches coinciding with the subdivision of the frontal nerve, to be annexed by the ophthalmic artery lying below the optic nerve. Another arterial ring, which transfers the internal maxillary artery to the outer side of the mandibular nerve root, is seen on the left side of the embryo. The stem of the stapedial artery has been interrupted just distal to its parent hyoid artery, and the maxillomandibular division of the stapedial has become the stem of the definitive middle meningeal artery. ×12.

Fig. 36. (No. 6203, 39 mm.) The adult configuration of the ophthalmic artery is recognizable on the left side of this embryo, and the stapedial artery has been completely taken over by the internal maxillary and ophthalmic arteries. On the right side of the embryo, the arterial ring around the optic nerve persists; on the left, interruption of the ring allows the ophthalmic artery to pass dorsal to the nerve. On both sides the ophthalmic artery has retained and augmented the orbital end of the supraorbital division of the stapedial to form its lacrimal branch. The remainder of the supraorbital division, lateral to the Gasserian ganglion, is incorporated in the middle meningeal artery. ×10.8.

These seven embryos also illustrate the development of the anterior cerebral artery. This forms as a collateral of the primitive olfactory artery (figs. 30–33), components of which are ultimately incorporated in the adult striate branches of the anterior cerebral (figs. 33–35). The medial striate artery (figs. 35, 36) is relatively constant in the adult; the variable striate branch found on the first part of the adult anterior cerebral is a remnant of the original stem of the primitive olfactory artery (right side of embryo, fig. 36).

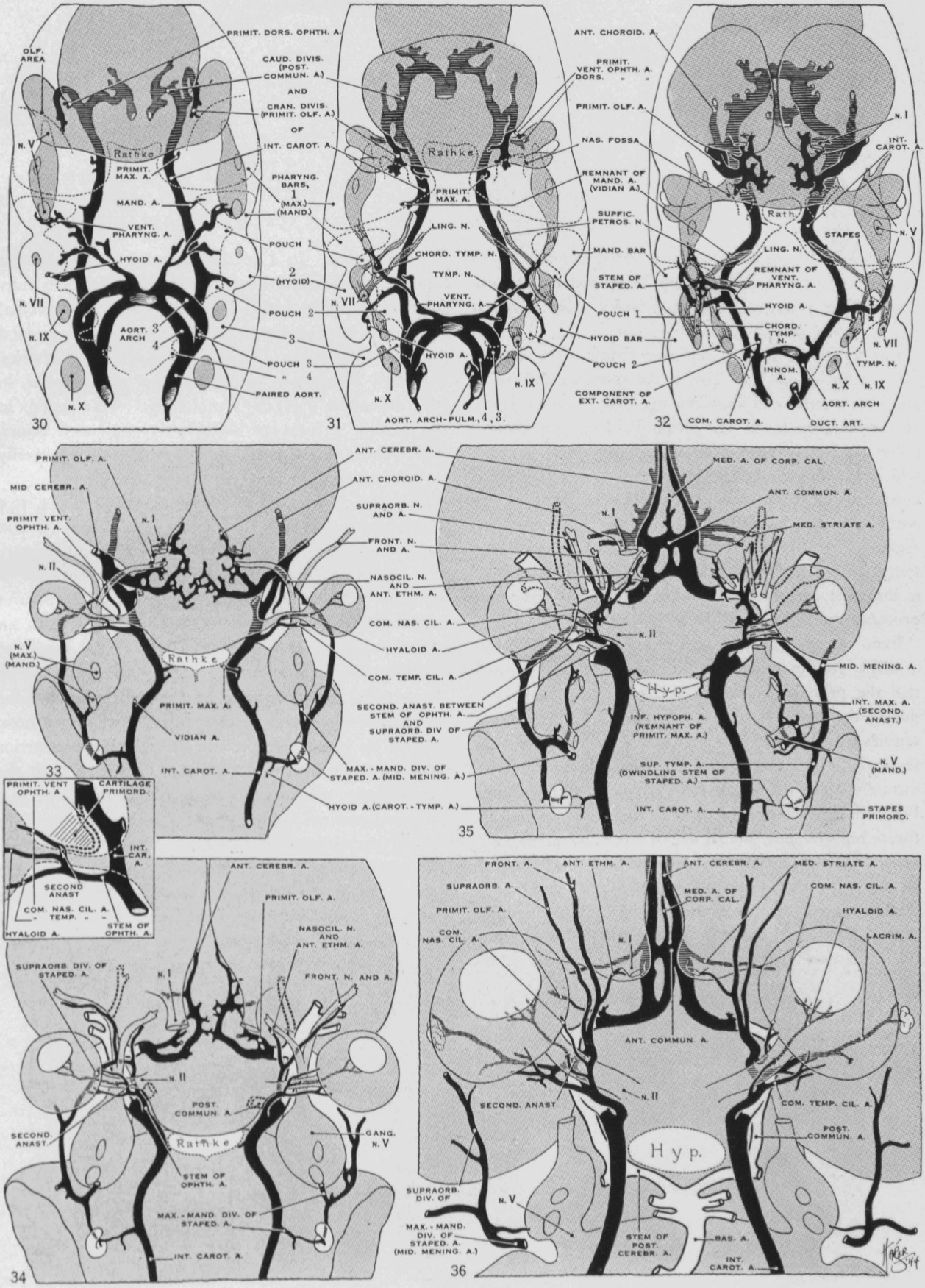

OLF. AREA
N. V
N. VII
N. IX
N. X
PRIMIT. DORS. OPHTH. A.
CAUD. DIVIS. (POST. COMMUN. A.) AND CRAN. DIVIS. (PRIMIT. OLF. A.) OF INT. CAROT. A.
Rathke
PRIMIT. MAX. A.
MAND. A.
VENT. PHARYNG. A.
HYOID A.
AORT. ARCH
PAIRED AORT.
30
PHARYNG. BARS, 1 (MAX.) (MAND.)
POUCH 1
2 (HYOID)
POUCH 2
3
POUCH 3
" 4
LING. N.
CHORD. TYMP. N.
TYMP. N.
VENT. PHARYNG. A.
AORT. ARCH-PULM., 4, 3.
31
ANT. CHOROID. A.
PRIMIT. VENT. OPHTH. A. DORS. " "
PRIMIT. OLF. A.
NAS. FOSSA
REMNANT OF MAND. A. (VIDIAN A.)
SUPFIC. PETROS. N.
MAND. BAR
STEM OF STAPED. A.
POUCH 1
HYOID BAR
POUCH 2
COMPONENT OF EXT. CAROT. A.
Rath.
STAPES
REMNANT OF VENT. PHARYNG. A.
HYOID A.
CHORD. TYMP. N.
INNOM. A.
COM. CAROT. A.
DUCT. ART.
AORT. ARCH
TYMP. N.
INT. CAROT. A.
32
PRIMIT. OLF. A.
MID CEREBR. A.
PRIMIT VENT. OPHTH. A.
N. I
N. II
N. V (MAX.) (MAND.)
Rathke
PRIMIT. MAX. A.
VIDIAN A.
INT. CAROT. A.
ANT. CEREBR. A.
ANT. CHOROID. A.
SUPRAORB. N. AND A.
FRONT. N. AND A.
NASOCIL. N. AND ANT. ETHM. A.
COM. NAS. CIL. A.
HYALOID A.
COM. TEMP. CIL. A.
MAX. - MAND. DIV. OF STAPED. A. (MID. MENING. A.)
HYOID A. (CAROT. - TYMP. A.)
33
PRIMIT. VENT OPHTH. A
CARTILAGE PRIMORD.
INT. CAR. A.
SECOND ANAST
COM. NAS. CIL. A.
" TEMP. " "
HYALOID A.
STEM OF OPHTH. A.
MED. A. OF CORP. CAL.
ANT. COMMUN. A.
MED. STRIATE A.
Hyp.
INF. HYPOPH. A. (REMNANT OF PRIMIT. MAX. A.)
SECOND. ANAST. BETWEEN STEM OF OPHTH. A. AND SUPRAORB. DIV OF STAPED. A.
SUP. TYMP. A. (DWINDLING STEM OF STAPED. A.)
INT. CAROT. A.
MID. MENING. A.
INT. MAX. A. (SECOND. ANAST.)
N. V (MAND.)
STAPES PRIMORD.
35
ANT. CEREBR. A.
PRIMIT. OLF. A.
NASOCIL. N. AND ANT. ETHM. A.
FRONT. N. AND A.
SUPRAORB. DIV. OF STAPED. A.
POST. COMMUN. A.
SECOND. ANAST.
GANG. N. V
STEM OF OPHTH. A.
MAX. - MAND. DIV. OF STAPED. A.
INT. CAROT. A.
34
FRONT. A.
ANT. ETHM. A.
ANT. CEREBR. A.
MED. STRIATE A.
SUPRAORB. A.
MED. A. OF CORP. CAL.
COM. NAS. CIL. A.
PRIMIT. OLF. A.
HYALOID A.
COM. NAS. CIL. A.
LACRIM. A.
ANT. COMMUN. A.
SECOND. ANAST.
COM. TEMP. CIL. A.
POST. COMMUN. A.
Hyp.
SUPRAORB. DIV. OF
MAX. - MAND. DIV. OF STAPED. A. (MID. MENING. A.)
STEM OF POST. CEREBR. A.
BAS. A.
INT. CAROT. A.
36

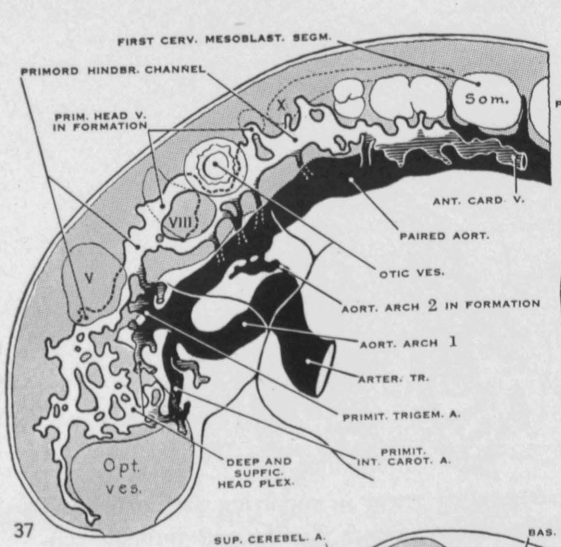
Plate 4

Lateral and horizontal (ventral view) reconstructions of four embryos to illustrate the formation and significance of the primitive trigeminal artery. (See also text figs. 1, 3; and pl. 5.)

Fig. 37. (No. 2053, 3 mm., 20 somites. See coronal view in fig. 43, pl. 5.) This is the youngest embryo of the present series and illustrates the most primitive vascular system of the head. The primordial hindbrain channel (shown white because it serves temporarily as a vein), which has already developed fragments of the primary head vein on either side of the otic vesicle, is fed by aortic sprouts concentrated in the trigeminal and otic regions. The first aortic arch gives off the primitive internal carotid and the primitive trigeminal artery, which is the most constant and conspicuous of the temporary presegmental branches of the paired aorta. ×60.

Figs. 38, 39. (Lateral and ventral views of no. 836, 4 mm.) At this stage the third aortic arch has formed, and the primordial hindbrain channel has disappeared during the evolution of a recognizable system of cranial arteries and veins (note that the primary head vein, shown white, is fully formed). The primitive internal carotid supplies the optic vesicle, forebrain, and midbrain. Plexiform fragments of a vascular tract, representing the future bilateral longitudinal neural artery, lie on the hindbrain wall and are fed by aortic presegmental branches in the trigeminal, otic, and hypoglossal regions. Since the first aortic arch has been replaced by the succeeding mandibular artery, that part of the aorta giving origin to the trigeminal artery is now considered a part of the internal carotid. In a succeeding stage, shown in text figure 1, the bilateral longitudinal neural artery is fully formed; its cranial end is supplied by a large trigeminal artery and its caudal end by the first cervical segmental artery, reinforced by the otic and hypoglossal arteries. The early obliteration of the primitive otic vessel is, in part, dependent upon the consolidation of the neurals in the mid-line to form the basilar artery, and their coincident withdrawal from the carotid, which arches laterally in this region (text figs. 1, 2). ×33.3.

Figs. 40, 41 (lateral and ventral views of no. 544, 11.5 mm.), and 42 (no. 940, 14 mm.; see lateral view in text fig. 6). Late persistence of the primitive trigeminal artery as a large caroticobasilar anastomosis in two embryos of the early postbranchial period. As shown in text figures 2 and 3, the trigeminal artery usually disappears at an earlier stage, and as soon as its role of cranial supply to the bilateral neural artery (or basilar artery, formed by the neurals) is taken over by the definitive posterior communicating artery. In the atypical cases shown here, it is to be noted that the caudal end of the posterior communicating artery is small at its junction with the basilar artery, which is still being supplied in large part by the trigeminal branch of the carotid. On the right side of the embryo in figure 41, however, where the trigeminal artery is only indirectly connected with the caudal end of the basilar, the posterior communicating artery is characteristically large throughout its whole length. (Carotid and posterior communicating arteries shown in white to permit view of arteries beneath.) ×15.



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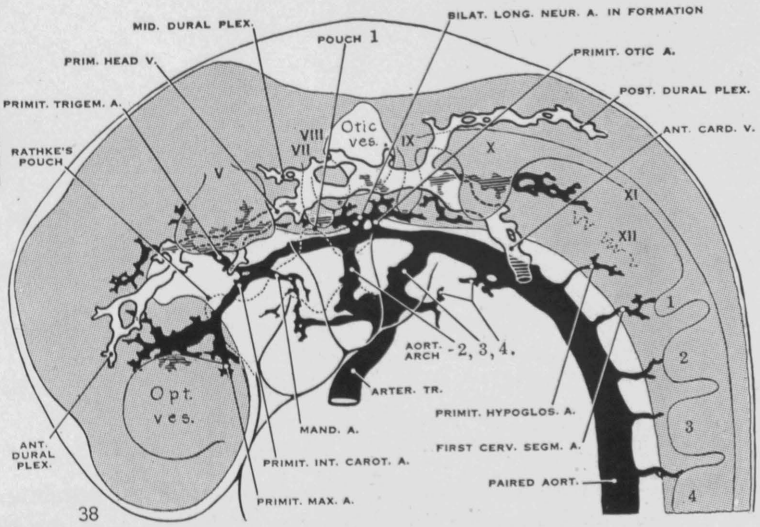

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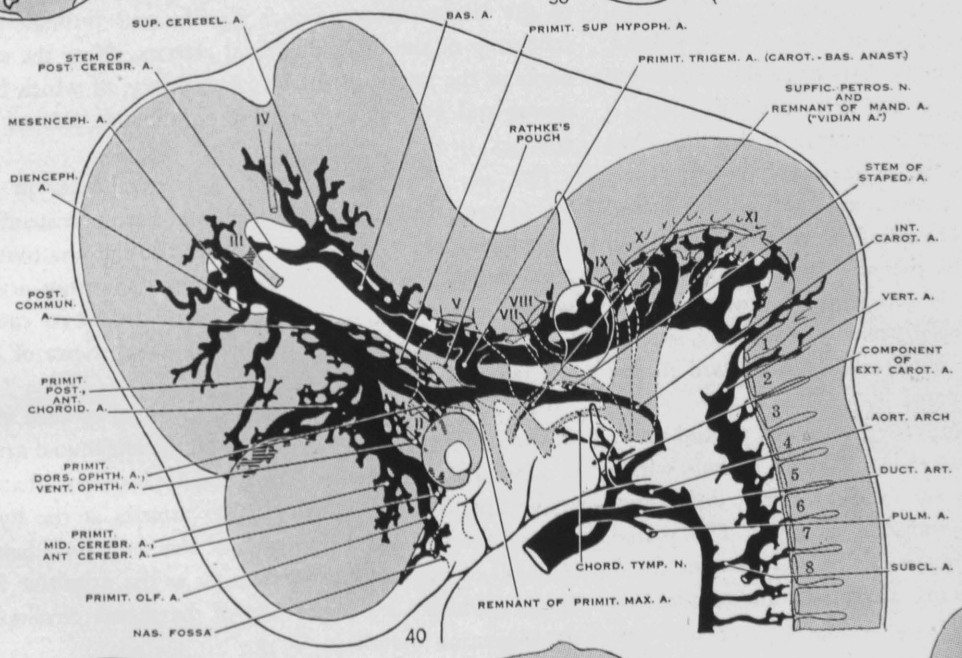

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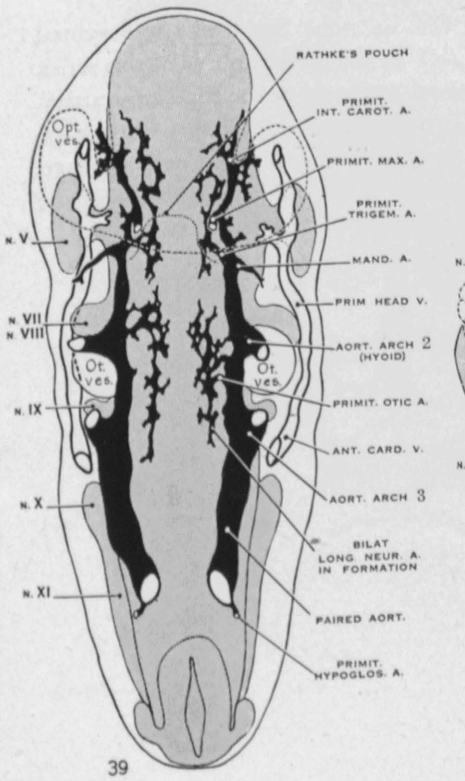

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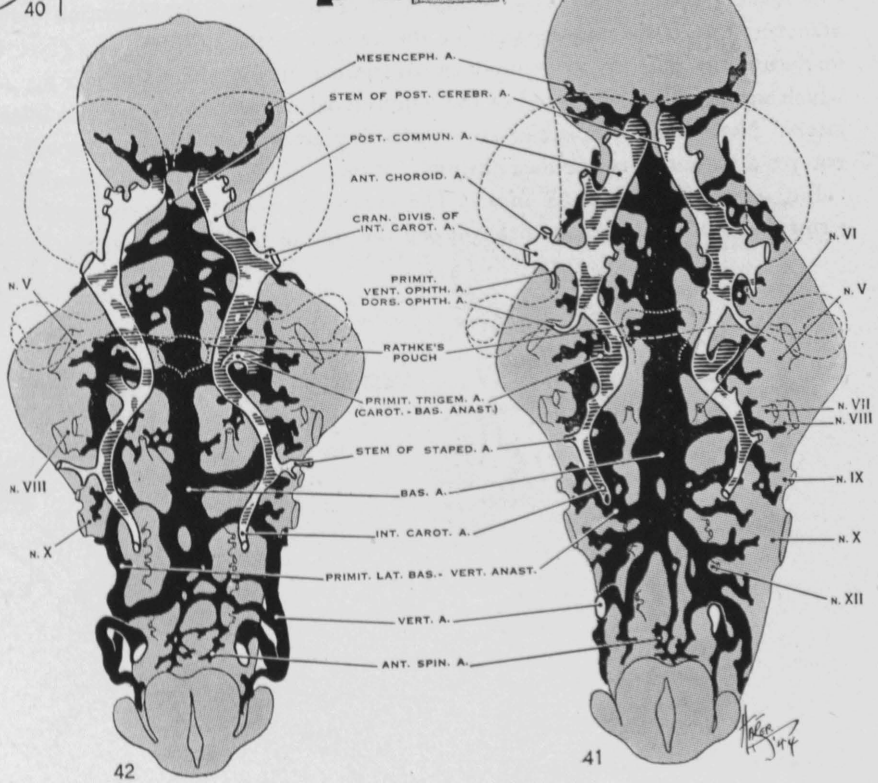

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Plate 5

Partial coronal reconstructions of six embryos from 3 to 43 mm., illustrating the origin and fate of the temporary trigeminal artery. Each is viewed from behind, as if sectioned at the level of the hypophyseal diverticulum and fifth nerve (excepting the first embryo, which is viewed just behind the eighth nerve), so that the right side of the picture shows the right side of the embryo.

Fig. 43. (No. 2053, 3 mm., 20 somites. See lateral view in fig. 37, pl. 4.) The primitive internal carotid, in its present origin from the paired aorta at the first aortic arch and in its course, is mesial in contrast with the primitive trigeminal artery, which arches laterally, supplying the head plexus en route to its termination in the primordial hindbrain channel. ×60.

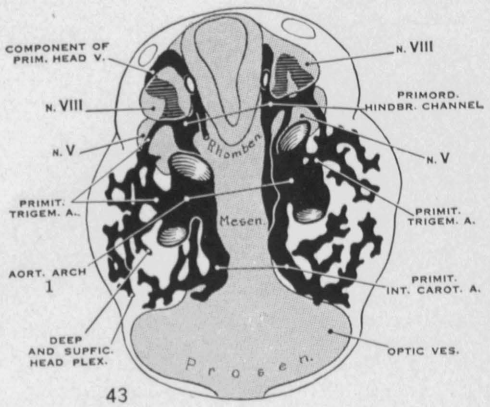
Fig. 44. (No. 588, 4 mm. See lateral and ventral views in text fig. 1.) The bilateral longitudinal neurals which precede the basilar artery are an end result of differentiation of the primordial hindbrain channel. The paired aorta of the preceding embryo (fig. 43) is now the internal carotid artery, following the involution of the first two aortic arches. It divides at Rathke's pouch into two branches: one is the prolongation of the carotid to the forebrain; the other is the temporary trigeminal artery, which supplies the cranial end of the longitudinal neural artery. Note that the posterior communicating artery is not yet a definitive continuous channel. ×40.

Fig. 45. (No. 1121, 11.8 mm.) The completed posterior communicating artery has usurped the role of the primitive trigeminal artery in supplying the cranial end of the basilar artery, which has formed through consolidation of the bilateral neural arteries. Note the remnants of the interrupted trigeminal artery, of which both dorsal and ventral ends persist on the left side of the embryo. ×15.

Fig. 46. (No. 940, 14 mm. See lateral view in text fig. 6; ventral view in fig. 42, pl. 4.) Late persistence of the trigeminal artery as a large caroticobasilar anastomosis after completion of the posterior communicating artery, which, as a result, is unusually attenuated at its caudal junction with the basilar artery (see other views of this embryo noted above). ×15.

Fig. 47. (No. 966, 23 mm. See coronal or face view of head in text fig. 9.) At this stage the trigeminal artery is sometimes represented by a small plexiform channel connecting the carotid and basilar arteries at the hypophyseal level. On the right side of this embryo, a basilar remnant of the artery extends as far as the primitive fold of dura which later forms part of the sheath enveloping the Gasserian ganglion. ×15.

Fig. 48. (No. 886, 43 mm. See lateral and ventral views in text fig. 10.) In the oldest embryo of this series, there are also bilateral remnants of the trigeminal artery. These terminate at the condensation of mesenchyme extending laterally from the primordial sphenoid cartilage, and presumably persist in the adult as branches of the basilar artery to the region of the fifth nerve. ×6.



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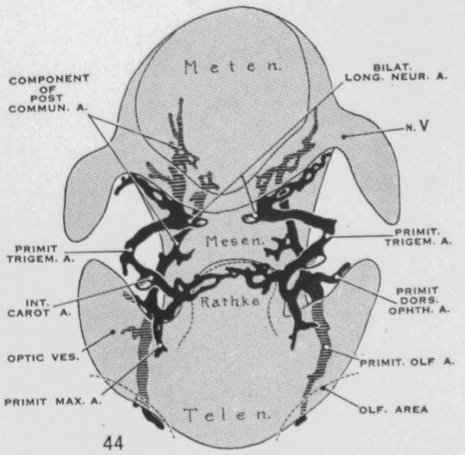

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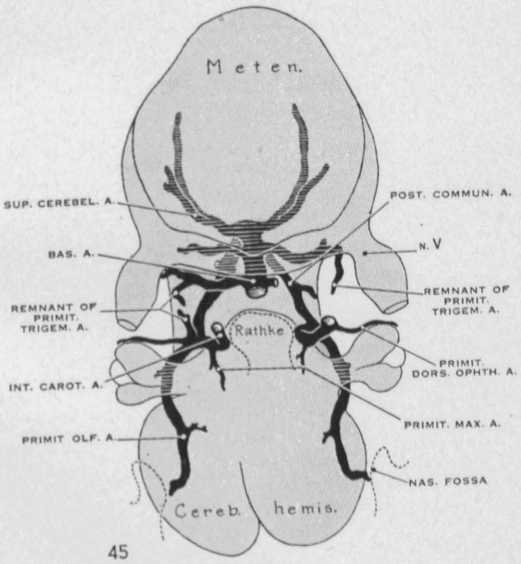

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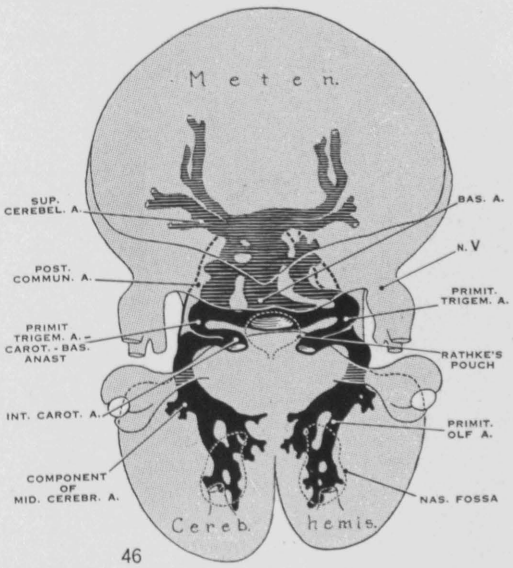

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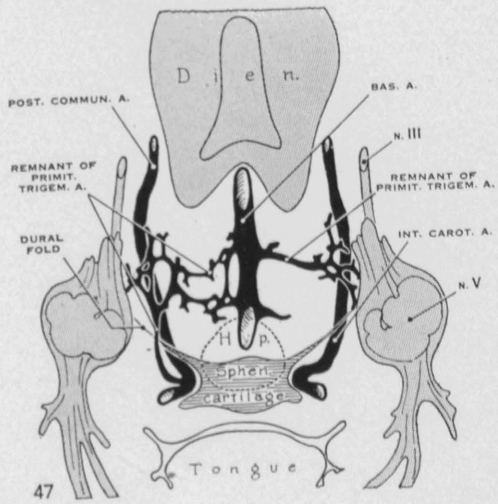

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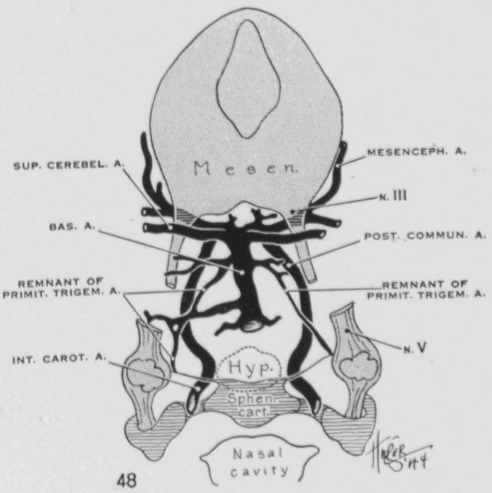

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